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SERUM IRON AND IRON-BINDING CAPACITY IN CLINICAL DIAGNOSIS

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Physiologic Considerations:

In 1923, Abderhalden, in his "Lehrbuch der physiologischen Chemie," stated that serum was practically free of iron[1]. Two years later, two French investigators analyzed horse serum in large quantities and found the concentration of iron which was not bound to hemoglobin to be about 0.2 mg. per 100 ml.[2] Results of the same order of magnitude were, in 1957, reported from 3 different laboratories, quite independently of one another, applying different analytical methods to serum of humans, as well as of certain animals[3-5]. Due to technical difficulties inherent in the minute quantity of iron normally present in plasma, as contrasted to the large amount of iron contained in hemoglobin of the red cells (See Fig. 1), it was not until about 1937 that a practical method for serum (plasma) iron measurement was published.[6] The necessary tool was now available to determine the physiologic significance and variations of the serum iron level and its changes in disease.

In most methods used for serum iron analysis, the proteins are precipitated at acid reaction and filtered or centrifuged off (Fig. 2, B); the iron in the filtrate, rendered bivalent by means of a suitable reducing agent, is determined photometrically after addition of a compound capable of forming a stable colored complex with ferrous ions (o-phenanthroline[7], 2,2′-dipyridyl[8]). In the author's modification[9] of Ramsay's method[10], a single stable reagent affords both protein precipitation and formation of the final color compound.* Thus, aside from the requirement of acid-washing of all glassware and the use of demineralized (iron-free) water, serum iron measurement poses no greater technical problems than the usual chemical blood analyses routinely performed in a clinical laboratory.

As early as 1927 Barkan showed that the iron in serum was non-dialyzable at the pH of the blood[3], but after acidification iron appeared in the ultrafiltrate, indicating that the metal had previously been bound to protein[11]. Subsequently, it was found that after intravenous injection of iron, the serum iron level could rise only up to a certain point ("braking effect"), i.e., about 300 mcg. per 100 ml.[12-14], even when the amount of iron injected was calculated to result in much higher concentrations. Signs of intoxication often appeared if the iron injection was continued after this saturation limit had been reached[14]. The limitation of the iron-binding capacity of serum

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* Reagent: 0.004% of 2:2′:2″-tripyridine and 0.05% of hydroxylamine HCl in acetate buffer, 0.5 M, pH 5.

A 4:1—reagent:serum mixture is heated to 100° C.; the optical density of the clear protein-free filtrate is proportional to its iron content.

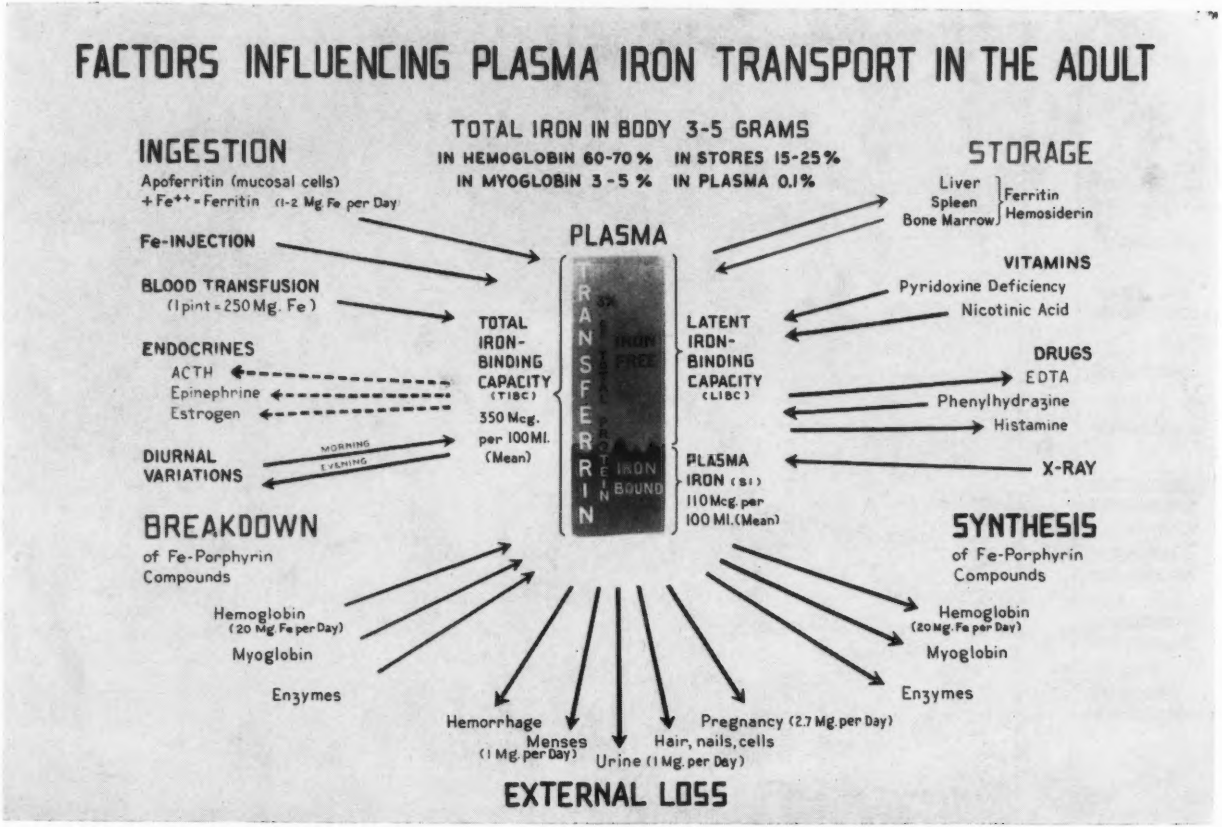

FIGURE 1. Arrows indicate direction of iron movement.

could also be demonstrated by *in-vitro* experiments in which ferrous salts were added to serum; there was no reaction with 2:2'-dipyridyl until the saturation limit was exceeded[15]. Further evidence confirming the iron-binding property of certain proteins stems from the observation that the growth of certain bacteria, which require ionic iron for their metabolism, was inhibited upon addition of egg white to the media[16]. Cohn's plasma fraction IV—3,4[17] was subsequently singled out as containing the specific iron-coupling globulin, since it was shown to be the only fraction capable of inhibiting *Shigella dysenteriae*[18].

Thus, iron is normally carried in the plasma exclusively by the iron-binding globulin, also called transferrin or siderophilin. This globulin, which has been obtained from subfraction IV—7[19] in crystalline state[20], has been identified electrophoretically as a beta-globulin[21]. This fact can be readily demonstrated with serum to which a trace of Fe^{59} has been added: The only segment of the paper-electropherogram which shows radioactivity is the β_1-globulin[22]. It has a molecular weight of about 90,000 and contains carbohydrates but no lipids; each molecule combines with 2 iron atoms. The iron is present in the ferric state[20,21], conversion of intestinally absorbed (or *in-vitro* added) ferrous ions occurring rapidly as they enter the plasma (or serum) in the presence of oxygen[21]. The Fe-transferrin complex is stable only within a small range of pH (7.25-7.50), the iron readily dissociating from the complex below and above this range[23].

Quantitative measurement of transferrin is possible by means of two fundamentally different technical principles: One involves estimation of the iron-binding capacity of serum or plasma ("Indirect Methods," Fig. 2,A), in accordance with experiments mentioned above[15]; the other ("Direct Method," Fig. 2,A) is based on a precipitin reaction with anti-transferrin rabbit serum[24]. A number of methods based on the first-named principle have been published, including procedures using radioactive iron[25]. A simple *"in-vivo"* method (Fig. 2,A 1) depends upon the intravenous injection of an amount of iron somewhat in excess of the total binding capacity of the available plasma volume (usually 10 mg. of elemental iron in adults) and determining the total iron content of serum harvested 5 minutes later[26]. Since all excess iron leaves the blood stream rapidly and enters the tissues (where it probably attaches to a protein with iron-binding properties, such as ferritin), the result represents the total iron-binding capacity (TIBC) of serum, expressed in mcg. of iron. The time-honored method of adding a ferrous salt drop-wise to serum in a test tube until the salmon-pink color of the Fe-transferrin complex (wave length 465 $m\mu$) develops and remains stable (Fig 2, II, 1)[18,23] is giving way to more expedient methods of analysis[27,28]. The above *"in-vivo"* method can be simulated advantageously by a test tube technique, in which ferrous ions added to serum or plasma in excess of the saturation limit are removed by means of a specific resin[10,28] (Fig. 2, II, 2B). With different modifications of the TIBC—determining principle, the mean value was, in different laboratories, reported to be between 300 and 360 mcg. of iron per 100 ml.[28-30].* These values correspond to 0.24 to 0.28 gm. of transferrin per 100 ml. of serum.** The quantitative precipitin reaction yielded a similar figure, namely, 0.27 gm.[24]. Hence, transferrin constitutes about 3% of the total protein of normal human serum, or about 20% of its beta-globulin fraction[29-33].

While all of the non-hemoglobin iron in plasma (SI) is bound to transferrin, from 50 to 80 percent of this protein are normally free of iron, constituting the latent iron-binding capacity (LIBC) of serum; LIBC + SI = TIBC (Fig. 1 and 2)[27-33]. This excess of unbound transferrin may, teleologically speaking, be considered a safety device capable of binding

*The mean ± 1 standard deviation was 346 ± 32 in the author's experience[10].

**Transferrin (mol. weight): iron (atom. weight X 2)=transferrin (gm. per 100 ml.): TIBC (gm. per 100 ml.), or 90,000 : 112=x : 0.0003. x=0.241 gm. per 100 ml.

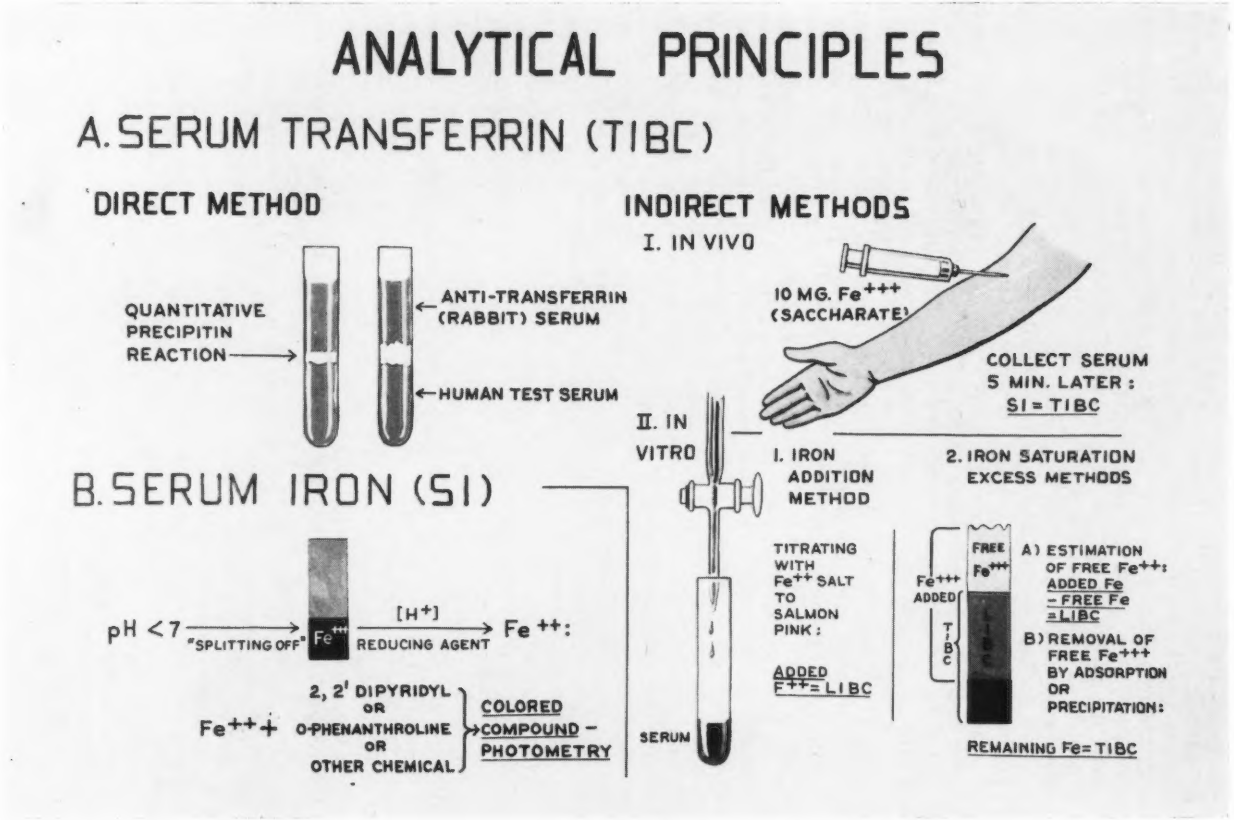
ANALYTICAL PRINCIPLES
A. SERUM TRANSFERRIN (TIBC)
DIRECT METHOD
QUANTITATIVE PRECIPITIN REACTION
ANTI-TRANSFERRIN (RABBIT) SERUM
HUMAN TEST SERUM
INDIRECT METHODS
I. IN VIVO
10 MG. Fe+++ (SACCHARATE)
COLLECT SERUM 5 MIN. LATER: SI = TIBC
II. IN VITRO
1. IRON ADDITION METHOD
2. IRON SATURATION EXCESS METHODS
TITRATING WITH Fe++ SALT TO SALMON PINK:
ADDED Fe++ = LIBC
SERUM
FREE Fe+++
Fe+++ ADDED
TIBC
LIBC
A) ESTIMATION OF FREE Fe++: ADDED Fe - FREE Fe = LIBC
B) REMOVAL OF FREE Fe+++ BY ADSORPTION OR PRECIPITATION:
REMAINING Fe = TIBC
B. SERUM IRON (SI)
pH < 7
"SPLITTING OFF"
Fe+++
[H+]
REDUCING AGENT
Fe++:
Fe++ +
2, 2' DIPYRIDYL OR O-PHENANTHROLINE OR OTHER CHEMICAL
COLORED COMPOUND - PHOTOMETRY

FIGURE 2

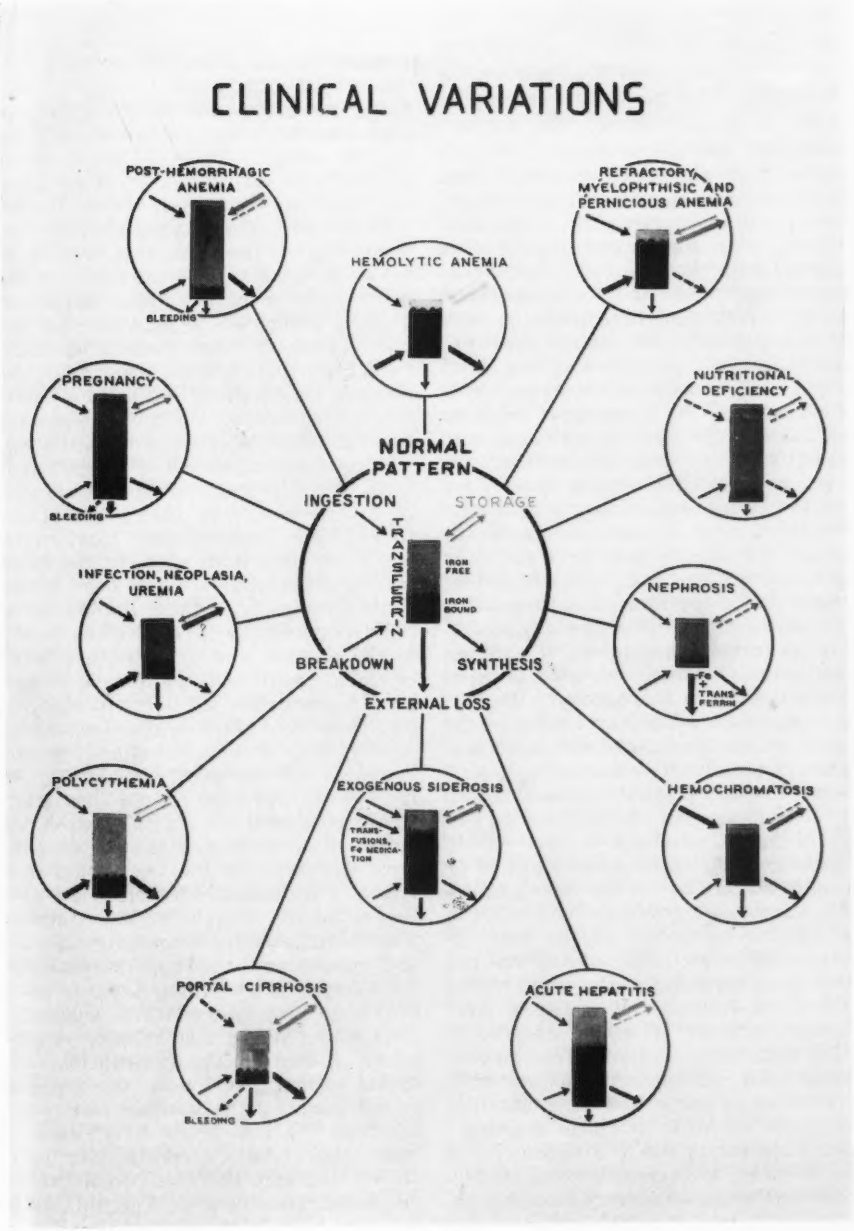
CLINICAL VARIATIONS
POST-HEMORRHAGIC ANEMIA
BLEEDING
HEMOLYTIC ANEMIA
REFRACTORY, MYELOPHTHISIC AND PERNICIOUS ANEMIA
PREGNANCY
BLEEDING
NUTRITIONAL DEFICIENCY
NORMAL PATTERN
INGESTION
STORAGE
TRANSFERRIN
IRON FREE
IRON BOUND
INFECTION, NEOPLASIA, UREMIA
NEPHROSIS
TRANS FERRIN
BREAKDOWN
SYNTHESIS
EXTERNAL LOSS
POLYCYTHEMIA
EXOGENOUS SIDEROSIS
TRANS-FUSIONS, Fe MEDICATION
HEMOCHROMATOSIS
PORTAL CIRRHOSIS
BLEEDING
ACUTE HEPATITIS

FIGURE 3

extra iron that might suddenly be put out by the tissues into the blood stream[31]. There is, of course, normally a constant flow of iron from tissues to plasma and back into tissues, causing a never-ending fluctuation of the plasma iron level. The latter, in fact, represents the moment-to-moment balance between iron absorbed from the gastrointestinal tract, that coming from catabolism of hemoglobin and other porphyrin compounds and returning to bone marrow and other tissues for synthesis of these compounds, and that going to and from the tissue stores; excretion of iron normally plays an insignificant part in the dynamic equilibrium of the plasma iron level (Fig. 1). The normal pre-breakfast range of plasma iron is about 50 to 180 mcg. per 100 ml.[10,28-33], varying somewhat with laboratories and analytical methods, the mean level in adults being about 110± 32[10] (1000 times less than glucose!). Significantly lower normal values in the female than in the male were found by some authors[29,30,32] but not confirmed by others[33-35]. Low normal levels occur during most of childhood [29]. The morning plasma level is usually the highest of each 24-hour period, a progressive drop of up to 30% occurring in the course of the day, followed by a gradual increase during the night. This diurnal variation[36] is normally not materially altered by ordinary food intake, but iron medication, whether oral or intravenous, will readily raise the serum iron up to the saturation limit[26,29-33,37]. The diurnal changes are accompanied by parallel fluctuations of the serum bilirubin, suggesting a rhythmic fluctuation in hemoglobin catabolism as the cause of both variations[36]. This fluctuation has been found abolished, at least with regard to iron, in instances of increased bone marrow activity (various anemias)[38]. Other factors, such as vitamins and hormones, may influence the plasma iron level; thus, nicotinic acid administration has been noted to produce a prompt though temporary rise in both serum iron and bilirubin, nicotinamide being ineffective[39]. Pyridoxine deficiency results in inhibition of bone marrow activity and hyperferremia[29]. The reverse, in turn, has been reported to be induced by epinephrine, estrogen, ACTH[29], and cortisone[40] (Fig. 1).

Clinical Considerations:

In view of the large number of physiologic and pharmacologic factors influencing the plasma iron level—which can in part only be clearly defined at our present state of knowledge (Fig. 1)—the wide normal range quoted above is not surprising. At the same time, this range evidently detracts from the utility of the serum iron level in clinical diagnosis. Thus, a finding of 60 mcg. per 100 ml. may reflect the usual level in one individual but represent an abnormally low value, attributable to recent blood loss, in another, whose "normal" concentration has been 120. Furthermore, the possibility of mutual potentiation or attenuation of 2 or more factors operative concomitantly must be considered at all times. Thus, hyperferremia may, on occasion, be compatible with chronic blood loss in a patient suffering from pernicious anemia. With these limitations in mind, one may say that loss or decreased intake of iron, low iron stores, and accelerated synthesis of ferro-protoporphyrin compounds are likely to result in hypoferremia, while augmented intake of iron, high stores, and either reduced synthesis or increased breakdown of hemoglobin will have the opposite effect. These postulates do not fully cover all empirical observations: Among the foremost exceptions is the low serum iron typically associated with chronic infection or uremia in spite of reduced hemoglobin synthesis and frequently high tissue stores, and the hyperferremia of acute hepatitis which may occur in spite of a co-existing systemic iron deficiency. Excessive binding and release, respectively, of iron by tissues (reticuloendothelial system, liver) must therefore be included among the possible factors influencing the iron level[29-35]. Release of iron from hepatic ferritin has been shown experimentally to occur under anaerobic conditions[41]. Ferritin itself has been found to circulate in the plasma of patients suffering from acute hepatitis, yellow atrophy or Hodgkin's disease

involving the liver[42]. Hence, under pathologic conditions associated with hyperferremia, transferrin may not be the only plasma protein carrying iron: ferritin and, perhaps, other proteins (globulins[43]) may take part. The analytical implications of these observations have not been fully investigated.

Deviations of transferrin from its normal level which have been described in various physiologic and disease states are far less amenable to functional interpretation than changes in ferremia. "The mechanism regulating the transferrin concentration is as little kown as the mechanism regulating the concentration of other serum proteins".[29] An increase has been found primarily in 3 conditions, i.e., the latter part of pregnancy, iron-deficiency anemia—whether incurred by loss (hemorrhage, pregnancies) or inadequate intake of iron—, and acute hepatitis[10,29,31,33,37,40,44]. In addition, high binding capacity has been reported in children aged 2½ to 10 years and in polycythemia[29], the latter finding remaining unconfirmed[10,33,40]. Hypotransferrinemia is frequently encountered in other types of anemia and in chronic infectious neoplastic, renal and hepatic disease (Fig. 3)[29-33,37,40]. In these instances, the decrease in transferrin is probably part and parcel of the systemic disturbance of protein metabolism, reflected in an altered plasma protein pattern which includes a decrease in albumin[29,31,33,40,45]. In (portal) cirrhosis and in hemochromatosis, the hypotransferrinemia is so marked and consistently present that it appears to constitute a "specific" deficiency, perhaps comparable to hypogammaglobulinemia and to the coeruloplasmin defect in Wilson's disease[33,45]. Loss of transferrin in the urine probably accounts for most of the transferrin (and iron) deficiency of the plasma in nephrosis[46].

"The regular increase of the transferrin concentration of the blood during iron deficiency and pregnancy strongly supports the assumption that the transferrin level is of importance for iron mobilization and absorption[29]." Laurell proposed that the relative concentrations of free and iron-bound transferrin influence the iron uptake by, or removal from, the various tissues, expressing this dynamic equilibrium by the equation:

$$\frac{\text{(Fe-transferrin)}}{\text{(Fe-free transferrin)}} = K.\ (Fe^{+++}).$$

This hypothesis, which has not found many followers[31], has subsequently been modified to include (apo)ferritin in the mechanism. Braunsteiner and his associates[40] postulated a dynamic balance between transferrin and the apoferritin of storage tissue, involving ready conversion of apoferritin to transferrin when the former's intracellular function is not utilized as a result of iron deficiency, and vice versa. Muirhead and coworkers[47] observed lowering of the elevated transferrin level in iron-deficient patients during intestinal absorption of oral ferrous sulfate and suggested consideration of 2 phases of transferrin, a circulating and a sequestered phase; in iron deficiency, the equilibrium would be shifted toward the circulating phase, producing a high TIBC and low SI; in hypotransferrinemic states, the sequestered phase may be favored. These speculations may perhaps be applied to the hypertransferrinemia of acute hepatitis, in addition to considerations of the well-recognized alterations of the plasma proteins in this disease which may comprise an increase in beta-globulin[45,48,49].

While the solution to these questions must await more extensive experimentation and clinical-pathologic correlation, it is apparent that the combined measurement of TIBC and SI is superior in diagnostic utility to that of SI alone[29,31,33,50], without adding substantially to the laboratory work load[10]. This is particularly true when applied to problems of anemia and of hepatic disorders. In a recent comparison of methods applied to assess the extent of iron stores in the body, measurement of the plasma iron and iron-binding capacity was found to be more reliable than oral iron tolerance tests and radio-iron studies in differentiating iron deficiency from other types of anemia, especially in patients with a hemoglobin below 9 gm. per 100

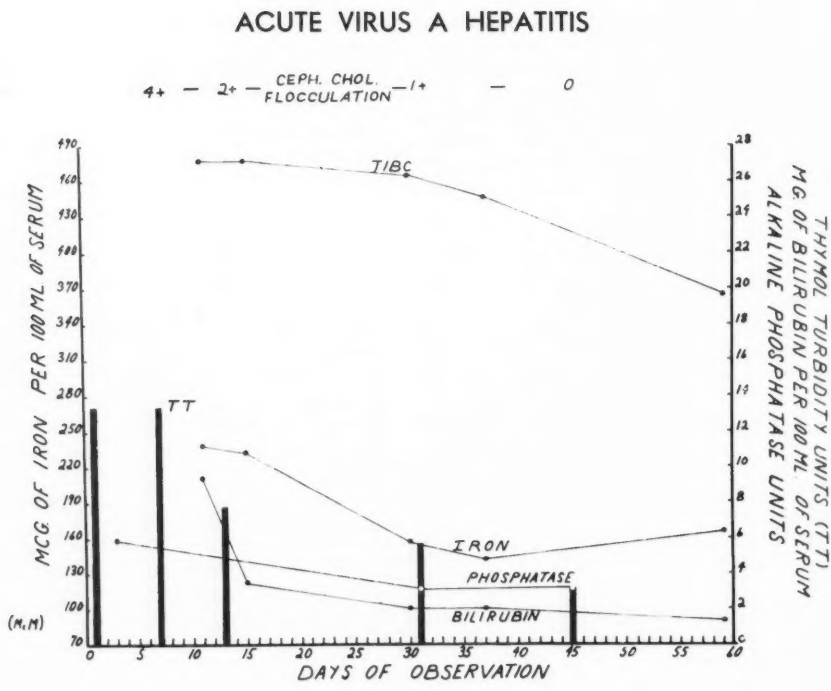

FIGURE 4

ml.[37]. It was surpassed in reliability only by examination of the bone marrow for stainable iron. The plasma iron determination alone was of little value.

Hence, the clinician faced with the finding of either a reduced hemoglobin or *hypoferremia*, or both, may receive a helpful directive from the *TIBC result*: an *elevation* strongly supports the diagnosis of iron deficiency; a *decrease* suggests a chronic—though perhaps inapparent—illness, such as infection, renal disease or cirrhosis. The combination of anemia with *elevated serum iron* usually implies impairment of hemoglobin formation (pernicious or hypoplastic anemias) or excessive hemolysis, conditions commonly associated with *low TIBC*[26,28,29,31-33]. In the presence of hepatomegaly and/or jaundice, the finding of a *high serum iron*[10,29,34,35,50] combined with *increased TIBC*[10,29,49] will favor the diagnosis of acute hepatitis (Fig. 4); it will point to hemochromatosis when *TIBC is low*,* especially when the latter is nearly or fully saturated[26,29,31,33,50]; rarely, the combination of *high SI* with *low TIBC* is encountered during a necrotizing phase of (portal, posthepatitic) cirrhosis. As a rule, however, the latter disease is characterized by a marked *decrease* of *TIBC* and a *normal* or *low SI*, findings which may also be encountered in prolonged biliary obstruction, especially when caused by neoplasm (Fig. 5)[10,26,29,31-35,50].

Even in the presence of a "non-descript" SI, detection of changes in TIBC may be no less helpful. Thus, an elevated TIBC may reflect the presence of an acute hepatitis even though SI may be quite normal. It should be further remembered that serial observations,

*With marked depression of TIBC to values below 200 mcg. per 100 ml., SI would be within its normal range and hence non-diagnostic without the concomitant TIBC measurement!

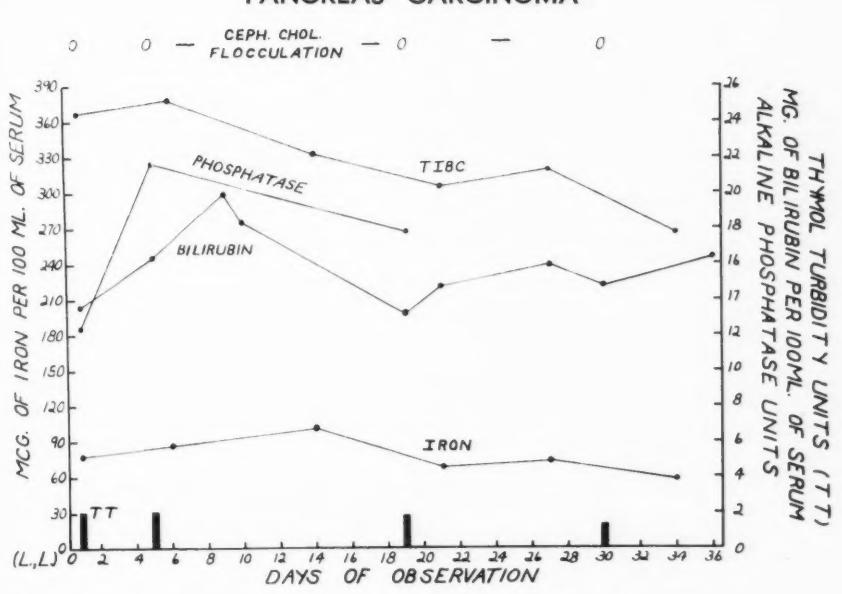

FIGURE 5

particularly in an acute disease, are likely to furnish a higher diagnostic yield than single examinations: Thus, in a patient with hepatitis, a significant increase in SI may not be recognized until the second or third week of the illness, the highest value either coinciding with, or following, the peak of the bilirubinemia[10,34,35,50]; TIBC may climb to its peak either simultaneously or with some delay, often forming a high plateau while SI and bilirubin return toward normal (Fig. 4)[10,49]. Finally, complicating diseases are bound to modify the diagnostic pattern of the SI and TIBC levels: for example, a chronic pyelonephritis in a patient with acute hepatitis will tend to depress and normalize both SI and TIBC which otherwise might be markedly elevated.

With these as with many other laboratory tests, full awareness of physiologic and pathologic influences is a prerequisite for their proper utilization and for avoidance of erroneous interpretation. Armed with this knowledge, the clinician will find serum iron and iron-binding capacity useful additions to his diagnostic arsenal.

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IN MEMORIAM

JACOB MARTIN ESSENBERG

Dr. J. Martin Essenberg, Professor of Microanatomy on the faculty of The Chicago Medical School from 1943 until his retirement in 1955, passed away at his home in Chesterton, Indiana, early in December, 1957.

Before joining the staff at The Chicago Medical School, Dr. Essenberg was on the faculties of The University of Missouri and The Stritch School of Medicine of Loyola University.

While on the faculty at The Chicago Medical School, Dr. Essenberg carried on studies that received national attention in the press. In particular, these were his investigations of the effect of cigarette smoke on the incidence of lung cancer in mice. He was one of the pioneers in this field which has since become a widely discussed issue.

Dr. Essenberg gave to The Chicago Medical School an exceedingly valuable embryologic collection which is now on display and which was recently dedicated as the Essenberg Embryonic Museum. Other material of this nature which he collected forms part of the embryological display at the Chicago Museum of Science and Industry.

Dr. Essenberg will be remembered by all who were associated with him at the School as one of the best-loved members of the faculty. He was a fine teacher as well as a scientist of stature.

CARCINOID AND ITS SECRETION — SEROTONIN

ROBERT BUSCH, M.D.*

The first specific description of these multifaceted entities was written by Lubarasch[1] in 1888 who reported two cases of multiple small ileal tumors and called them "atypical primary Carcinoma." In 1907 Obendorfer[2] referred to these as "carcinoid" because they supposedly folowed a benign course. At present most pathologists[3,4,5,6] are agreed that these are adenocarcinoma grade I (slow growing).

The progenitors of these neoplasms were identified in 1914 by Gossit and Masson[7] as the "Kulschitsky" or "Argentaffine" cells which exist normally in the bases of the crypts of Lieberkuhn throughout the intestinal tract from the cardia to the anus, and which are derived from neural crest ectoderm.

Their progeny may therefore appear anywhere in this wide expanse, although statistically, by far the greatest number arise in the appendix. The duodenum is the site least involved and up to November of 1957, only nineteen[8] authenticated carcinoids of the first part of the small intestine were described. Three of these exhibited metastatic masses at operation. At laporotomy for a duodenal tumor in December 1957, the author excised, in elliptical fashion, a small tumor mass, at approximately the junction of the first and second portion of the duodenum, which was pathologically an unquestionable "carcinoid".

The patient, a 41 year old well developed, well nourished, colored male, first noted marked dyspepsia two years prior to admission. This occurred one hour after eating. The symptoms abated with the use of antacids and bella-donna but recurred in force nine months before admission and were associated with marked pain and unrelated to food intake. X-rays revealed a smooth, circular, circumscribed filling defect in the proximity of the duodenal cap whose true nature was not pre-operatively entertained by the surgeon or the referring physician. Post-operative blood and urine specimens revealed no serotonin or breakdown products but the patient was given Phenergan® pre-operatively which may interfere with biochemical determination.** No metastases were noted at exploration and at present the patient is asymptomatic.

Chromaffine tumors are usually uniform in pattern resembling basal cell carcinoma and although some show markedly more pleomorphism and mitotic figures than others, differentiation cannot be made on a microscopic basis, between those which will, and those which will not metastasize[8].

These neoplasms are peculiar in many ways, not the least of these being their completely unpredictable course following discovery of gross and multiple intra-abdominal metastases. Rectal carcinoids particularly, follow the expected malignant pattern of progressive metastatic enlargement, debility and death (i.e. those 10% which metastasize). Other primary sites with large multiple metastases may lie dormant for extensive periods.[9]

Recently (1954) Thorsen[10,11] depicted a syndrome of broncho-constriction, unusual cyanosis, flushing, and disease of the endocardium and valves of the right heart in association with carcinoid accompanied by metastases to the liver.

These cells (both normal and tumor cells) evidently have the ability to utilize tryptophane in producing 5-hydroxytryptophane and further 5-hydroxytryptamine which is serotonin[12]. The latter's degradation product is 5-hydroxyindolacetic acid which is found in urine.

5-hydroxytryptamine is formed from platelet disintegration[13] and from breakdown of mast cells[11] in which process

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**Any Phenothiazine derivatives, personal communication, Dr. Horwitt, Biochemist, Mt. Sinai Hospital, Chicago.

heparin, histamine and protamine are also liberated. It is present in large amounts in carcinoids metastatic to the liver and is also found in the brain and blood.

Lembeck[14] first isolated large amounts of 5-hydroxytryptamine from a carcinoid at autopsy and this was identified as identical with "Enteramine" and serotonin[15]. This substance directly affects blood vessels, smooth muscle, and is a bronchoconstrictor. Cyanosis and flushing result from dilated capillaries and venules. Diarrhea and abdominal pain follow bowel hypermotility, and during attacks palpitation, tachycardia and dizziness may result[16].

It is interesting to note that since tryptophane is an essential amino acid, utilization of large amounts may result in a deficiency state accompanied by weight loss, muscle wasting, etc. It has been estimated that as much as 60% of the daily intake may be diverted by tumor to serotonin.

Analogous to what results in pheochromocytoma Sjoerdsma[17] stated that "Emotional disturbance, physical exertion, and manipulation of the tumor were the most consistent factors in precipitation of flushes."

This author also noted that feeding normal increased amounts of protein or typtophane did not increase 5-hydroxyindolacetic acid in urine (normal 2-9 mgm./day) but, those with carcinoid (malignant) (76-580 mgm./day) increased urinary outputs were noted with equal feeding.

A curious fact is the finding of increased amounts of serotonin in carcinomas of the bronchus, larynx and pyriform fossa. The significance of this is unknown at present.[18]

Among its diverse effects serotonin causes 1) increased gastric secretion and motility[12]. 2) It is supposedly destroyed in the lung (accounting for its pathologic effect on the right side of the heart) and although the relationship of pulmonary arteriovenous aneurysm to hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber disease) is generally accepted,[19] it was suggested only recently[20] that in arteriovenous shunts serotonin may escape detoxification and cause telangiectasia; 3) It is a pressor substance possibly related to hypertension[21]. 4) Its presence in the brain has directed a new and possibly "explosive" approach to schizoid treatment related to studies of indole containing substances. (Explosive because this investigative path may undermine the "functional" basis for explanation of mental aberration.) Lysergic acid diethylamide and adenochromes, which like serotonin contain the indole nucleus, are psychotomimetic. The hypothesis has been made that L.S.D. produces its behavior by interfering with the physiologic action of serotonin. The Rockefeller workers used the lock and key analogy.[11,12] The suggestion here is that too little serotonin produced psychic diversion. However, it is also postulated that too much may cause aberration. e.g. L.S.D. potentiates blood pressure rise in dogs, caused by serotonin. Reserpine reduced serotonin concentration in the body and only those Rauwolfia alkaloids which are tranquilizers have this depleting effect.[11]

To end, some extrapolations and questions have presented themselves.

A) Is it possible that in a certain percentage of irritable neurotic patients whose symptoms have been described to unusual stresses and strains of life we might find elevated 5-hydroxytryptamine levels endogenously or exogenously produced?

B) Can it be that all mental disease might be basically caused by indole-like or other chemical substances and that eventually antimetabolites might be furnished for each of these? Does shock therapy work by altering, physico-chemically, serotonin and would it be advisable to evaluate 5-hydroxyindole acetic acid urine levels post-shock?

C) In those patients with intractable recurrent ulcers, adequately treated both medically and surgically, is it worthwhile evaluating serotonin levels and exploring carefully for argentaffine tumors?

D) Does serotonin along with renin play a role in essential hypertension (having some association with so-called "Neurogenic" taking over of a transitory renin mechanism[23]) and could acceleration of ordinary chemical breakdown allow more vascular relaxation and perhaps a new approach to treatment? Does this account for Reserpine success in the treatment of some hypertensives whose pressure increase is possibly related to serotonin effects?

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MANAGEMENT OF MEDICAL RENAL DISEASES IN CHILDREN**

A. GROSSMAN, M.D.*

The management of any disease becomes easier when one knows the etiologic agent causing that disease and the patho-physiology involved. Certainly there are many causes of the syndrome which we recognize as acute glomerulonephritis, but it is doubtful that any one will disagree that in the majority of cases, the etiologic agent in children is the Group A Beta Hemolytic *Streptococcus*. This disease usually attacks children of school age, and after a latent period of 10 to 14 days following the *Streptococcus* infection it becomes clinically apparent with bloody urine, edema, or convulsions, alone or any combination thereof. In most series reported, certain few types of *Streptococci* were incriminated. (Table I). If this then is true and only these few types are responsible, it explains the commonly held clinical impression that acute glomerulonephritis does not recur in the same patient. Recurrence by another type is therefore theoretically possible, but very improbable.

Similarly, how the nephron is damaged is not settled. Many still feel that it is by direct action of the organism, its toxin or a combination thereof, but again while many mechanisms can acutely injure the renal glomerulus, most often, at least in children, it occurs as an antigen-antibody reaction affecting the glomerulus. Direct evidence for this concept is based on:

1) The latent period from the time of the Streptoccocal infection and the manifestations of acute glomerulonephritis.

2) The presence in the serum of a high titer of Streptococcal antibodies.

3) The fall of serum complement.

Indirect evidence for this concept includes 1.) the experimental production of this disease in animals using Nephrotoxic Sera and 2.) the demonstration of an accumulation of antigen in the glomerulus of autopsy material using "Coons" fluoroscein technique.

If then, acute glomerulonephritis, in the majority of instances, is the result of an antigen-antibody reaction to Beta Hemolytic *Streptococci*, prevention of this disease depends on prevention of Streptococcal infections which appear at this writing to be as much a problem for the economist, sociologist, and clergyman as for the physician. The treatment of Streptococcal disease, however, simply depends on adequate doses of penicillin over an adequate period of time. Many investigators have published the results of this problem. It can easily be deduced from these many studies that in young children, 300,000 units—and in older children, 600,000 units of Procaine penicillin every 3rd day for 10 days; or two injections of Benzathine penicillin (Bicillin C-R) 5 days apart, will in the majority of cases, adequately eradicate the Streptococcal infection. It is now well established, that eradicating the Streptococcal infection does not necessarily mean that acute glomerulonephritis will not develop. This is in sharp contrast to the current opinions regarding Rheumatic Fever.

Treatment of the acute nephritis itself will depend upon one's concept of the disease. Fortunately the natural history of the disease in children is such a favorable one, that we must hesitate to assess the effects of drugs or other remedies. At the present time, aside from rest in bed and eradicating the Streptococcal infection, treatment is symptomatic and aimed primarily at the following complications.

I. *Hypertension*, by itself poses the problem of interference, realizing full well that lowering the blood pressure

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TABLE I. SEROLOGIC TYPES OF STREPTOCOCCI ISOLATED FROM SPORADIC CASES OF ACUTE NEPHRITIS (1949-1956)

NUMBER OF PATIENTS	SEROLOGIC TYPES
62	12
15	4
1	25
2	12 and 19
1	1 and 6
1	19 and NT*
1	NT*

*Not typable with the available antisera.

might further reduce the glomerular filtration rate. This is an individual problem and varies with each case encountered. Certainly if one sees the blood pressure rising, attempts to lower it are mandatory. The signs and symptoms of hypertensive encephalopathy are too well known to warrant detailed description; it will suffice to mention listlessness, irritability, convulsions, nausea, vomiting, headache, and visual disturbances, just as a few. The drugs available today to reduce acute hypertension and/or hypertensive encephalopathy are Serpasil®, Apresoline®, Hexamethonium and $MgSO_4$. (Table II). We have been successful in almost all attempts to reduce the acute hypertensive emergency with Reserpine (Serpasil®). We give 2.5 mgs. intra-muscularly, and since its effect varies from 8 to 14 hours, it is given accordingly as necessary. In some cases of resistant hypertension, other investigators have reported the successful use of hydralazine hydrochloride (Apresoline®), 0.1 mg./Kg. and Serpasil®, 0.15 mg./Kg. given intra-muscularly in combination. The ganglionic blocking agents like Hexamethonium are more successful in dealing with chronic hypertension. In addition, toxic reactions have been encountered quite frequently. Intra-muscular magnesium sulfate has proven too painful, too unpredictable, and too toxic. The enthusiasm for intravenous magnesium sulfate originally suggested by Harris has not been sustained.

II. *Myocarditis,* with or without cardiac failure is one of the more difficult complications of acute nephritis to recognize. One must be on the lookout for unusual dyspnea and tachypnea, a rising pulse rate, and pulmonary congestion with rales in the chest. One may also find electrocardiographic changes suggesting myocarditis, and X-ray changes suggesting cardiac dilatation. This complication requires oxygen, sedation, salt restriction, and digitalis. Digitalization is done rapidly,; the dose is determined on the following schedule: 0.02 to 0.04 mgs./Kg. of digitoxin given in 3 divided doses intramuscularly on the first day, and then 0.1 of the digitalizing dose is given orally, daily for maintenance. Just a word about salt restriction. If one resorts to a so-called "salt-free diet," the child will refuse to eat entirely. This regimen will do more harm than good, so that we use a regular diet, but without an accessable "salt shaker." If the cardiac failure is due to hypertension, in addition to all other things, reducing the blood pressure is basic to good therapy.

III. *Severe oliguria or anuria,* is indeed one of the most trying complications of this disease. Fortunately this experience is not too frequently encountered, but when it does occur it is usually associated with a rapidly developing renal azotemia and hyperkalemia together with listlessness, vomiting and occasional coma. At this time one is faced with the problem of maintaining hydration, regulating electrolytes and pH, bleeding, and irreversible central nervous system dam-

age. Fluids are administered intravenously, giving, however, only the amount lost by insensible means which is approximately 600 milliliters per square meter per day, plus urinary output. If urinary output cannot be measured, we calculate on the basis of 1000-1500 ml. per square meter per day. We use a very hypotonic electrolyte solution certainly without any potassium; an example would be one part lactate, two parts saline, and seven parts 10% glucose in water with added calcium gluconate.

The ultimate outcome of acute glomerulonephritis is generally accepted to be an excellent one. Statistics from different groups studied, agree that 95 to 97 percent recover, 2 to 3 percent succumb, and 1 to 2 percent go on, progressively, to develop chronic glomerulonephritis. It is important to emphasize that only the very occasional case goes on to chronic renal disease. It is very well known that activity of the disease goes on beyond the time when the sedimentation rate or other phase reactors are elevated. This is best illustrated by the Addis count of the urine. In many cases, the Addis count is increased for as long as one year after the acute phase of the illness. Our principle has been to keep these children at home with some activity only until the sedimentation rate is normal, after which time they can return to school. We recommend an occasional examination of the urine, particularly an Addis count, if available. When the urine returns to normal, follow-up is no longer necessary. We certainly would not recommend prophylactic penicillin since there are so few nephritogenic strains of Streptococci that a second attack by another nephritogenic strain is extremely unlikely.

There is one form of acute glomerulonephritis which deserves separate discussion. Henoch-Schoenlein purpura is an antigen-antibody disease sometimes following infection with Group A Beta Hemolytic *Streptococci*. It is characterized by joint pain, abdominal pain, and an urticarial purpuric rash. Ten percent of children with this disease have acute nephritis. This form of acute nephritis has only recently been studied and the prognosis is not as good as the prognosis of ordinary acute glomerulonephritis. Its complications and treatment are the same, but since the prognosis is so much worse, the use of steroids should be con-

Management of Acute Hypertension

DRUG	DOSE	ROUTE	DURATION	TOXICITY
SERPASIL	2.5 MGS	I.M.	8-14 HOURS	+
APRESOLINE	.2 MG/KG	I.M.	12 HOURS	++
APRESOLINE	.1 MG/KG			
+		I.M.	24 HOURS	++
SERPASIL	.15 MG/KG			
MG SO_4	300-500 ML 3% SOLUTION	I.V.	?	+++
MG SO_4	.2 ML/KG OF 50% SOLUTION	I.M.	?	++++

TABLE II.

templated. Renal Biopsy in a few cases studied, one by us, revealed some of the changes in the renal glomerulus that one associates with early lupus nephritis. While the subject is not settled, at this time we recommend the use of steroids in this type of acute nephritis. The dose and duration would depend on when the acute phase reactors like the sedimentation rate, C-reactive protein, or mucoproteins return to normal.

One last word before leaving the subject of acute glomerulonephritis. Bates and Earle have recently described a mild outbreak of acute glomerulonephritis in a Navy installation which was certainly caused by an infectious agent other than the Group A Beta Hemolytic *Streptococcus*. They demonstrated a few subtle clinical differences between this group and a control group which was definitely associated with Group A Beta Hemolytic *Streptococci*. They also demonstrated some differences in the morphological manifestations between the two groups by Renal Biopsy.

Another common renal disease encountered in children is the Nephrotic Syndrome, the synonym of the more popular "Nephrosis." In children we believe that the Nephrotic Syndrome is usually a primary disease, in contra-distinction to adults where it is usually secondary to some other disease, i.e., Lupus Erythematosus, Amyloidosis, Diabetes Mellitus, etc. The Nephrotic Syndrome is clinically easily recognized by the following signs, symptoms, and laboratory findings:

It usually affects young children between 2 and 3 years of age, with facial or generalized edema, sometimes with ascites and hydro-thorax. The urine contains 4+ protein with or without formed elements like red and white cells as well as casts. The serum protein is usually markedly depressed below 5 gm. percent. This depressed serum protein is due primarily to the low serum albumin. The serum lipids are elevated, particularly cholesterol. The usual serum electrophoretic pattern is a depressed Albumin, normal Alpha Globulin, elevated Beta Globulin, and depressed Gamma Globulin. The blood pressure and urea nitrogen may or may not be elevated and usually are not. It has been frequently noted that formed elements in the urine, hypertension, azotemia, and depressed renal function do not necessarily mean a poor prognosis.

It is also well known that the Nephrotic Syndrome can develop from a variety of insults to the glomerulus and indeed in adults, the varieties are many. However, the classical Nephrotic Syndrome as seen in very young children, is considered by most pediatricians to be a distinct disease. It is hard for us to conceive that this disease in a 2 or 3 year old child was preceded by a disease (unrecognized acute glomerulonephritis), which is extremely rare before the age of five, and/or that it is a phase of a chronic disease at this young age. Similarly, and probably most important, using mortality statistics, it is hard for us to conceive that this disease, which has a 50% mortality without treatment, and probably less with treatment, could be a part or phase of a disease (chronic glomerulonephritis) in which the mortality is almost 100%. This syndrome, like acute glomerulonephritis, is considered by many to be an antigen-antibody disease. The evidence in favor of this concept is primarily based on:

1) Its experimental production in animals using Nephrotoxic Sera.
2) The accumulation of antigen picked up in greater quantity by fluorescein-stained antibody of glomeruli in autopsy material.
3) The depression of serum complement has often been noted in antigen-antibody reactions, it certainly is depressed in the Nephrotic Syndrome. The explanation that serum complement, being a protein, is lost in the urine, does not hold up since it has been repeatedly noted to be normal or super-normal just before diuresis ensues. Indeed diuresis can be predicted, when serum complement returns to normal.
4) The fact that this disease responds so well to steroid therapy which is believed to effectively block antigen-antibody reactions, and

5) In many instances manifestations of the Nephrotic Syndrome come on after a variable latent period following an upper respiratory infection.

What the antigen or antigens are, and the detection of their antibodies have not been demonstrated. Be this as it may, the successful management of this syndrome is based on the proper use of the steroid hormones and the prevention of exacerbations which are usually associated with infections by the expedient use of antibiotic or chemo-therapeutic agents. Rest in bed is not essential. Indeed if the patient can be at least partially ambulatory, the emotional impact of this disease is somewhat lessened. Some investigators have insisted on the use of a "salt-free diet," to accelerate the diuresis; but as we pointed out before, we settle for a normal diet without an accessible "salt shaker." Several of the steroids can be tried. We have used Cortisone and occasionally corticotropin. We use 300 mg. of Cortisone or 150 mg. A.C.T.H. per square meter per day for ten days; we use penicillin prophylactically during the period of steroid therapy and we give one or two grams of potassium daily. We then abruptly stop all medication. Diuresis may begin before steroid therapy is stopped, a few days later, or not at all. Diuresis, however, is not our main objective. We are more interested in a return to normalcy of the acute phase reactors, particularly the sedimentation rate, a rise in serum albumin and total serum protein, a fall in serum lipids and the disappearance of protein from the urine. If after a short wait (3 to 5 days) these are not accomplished, a second ten-day course of steroid therapy will be started, and if necessary a third course is given.

At times, if one has the clinical impression, based on many variables, that he is dealing with a more severe form of the disease, one can continue steroids daily until the desired goals are reached and then stop, either gradually or abuptly, depending on how many days it took to accomplish this goal. This method is suggested for all patients by some investigators in this field. Usually one or two ten-day courses of therapy are necessary and most often the average nephrotic will respond very nicely. One word of caution: after marked or unusual diuresis, one should be on the lookout for hyponatremia and/or hypokalemia. The problem of continued steroid therapy is not a settled one. It has been the experience in our group that with intermittent therapy the number of exacerbations have been cut to a minimum. We give our patients a three-day course of steroid therapy each week, again we give 300 mg. cortisone per square meter per day. We continue this intermittent prophylactic steroid therapy until we feel clinically that our patient has overcome this disease, that he is growing and thriving, and that certainly none of the clinical, urinary, or metabolic data which suggest activity of the disease is present. At times one is misled and relapses occur after therapy is stopped. Since intermittent

Steroid Therapy of Nephrotic Syndrome

DRUG	DOSE	ROUTE	DAY'S
CORTISONE	300 MGS/M^2/DAY	ORALLY	10 OR MORE
A.C.T.H.	150 MGS/M^2/DAY	I.M.	10 OR MORE
PREDNISONE	60 MGS/M^2/DAY	ORALLY	10 OR MORE
PREDNISILONE	60 MGS/M^2/DAY	ORALLY	10 OR MORE

TABLE III.

therapy may be necessary for a long time, the untoward reactions of prolonged steroid therapy should again be emphasized. Other investigators, however, do not believe intermittent steroid therapy is necessary. They feel that once a clinical and metabolic remission has occurred, no further treatment is necessary. Should an exacerbation occur they then employ full therapeutic doses of steroid therapy as required. Others, however, have recommended intermittent steroid therapy as we do.

The prognosis for complete recovery from the Nephrotic Syndrome is about 50 percent. Statistical studies on mortality since the advent of steroid therapy are now in progress and from preliminary reports it appears that the mortality is declining.

Just a few words about the patient with the Nephrotic Syndrome who does not respond to the usual therapeutic regimen—the refractory patient. It is quite possible that these are cases with more severely damaged glomeruli. Clinically and metabolically they resemble the patient with the Nephrotic Syndrome, but the similarity fades in their lack of response to the usual steroid regimen. It is likely that the damage to the glomerulus was too severe, beyond the stage of restoration by steroid medication. This concept has been fortified by the frequent clinical observation that these patients who do not respond, go on to progressive renal failure. At autopsy, one finds the changes associated with subacute or chronic glomerulonephritis. The crucial question that must be answered then is: Did the histological changes of sub-acute or chronic glomerulonephritis exist at the beginning of this illness? In other words, did this illness begin with such severe damage to the glomerulus, that the morphological changes one associates with long standing renal disease, were there to start. In our series studied by percutaneous renal biopsy we did find evidence of subacute glomerulonephritis early in the course of the disease.

It is with the refractory individual that one is occasionally compelled to use the following methods, which are ordinarily not recommended, to combat the edema and which are only of temporary benefit.

1) 300-400 ml. of 12 percent salt-free dextran per square meter per day for three to four days.

2) 15-25 grams of concentrated (25 percent) solution of human albumin can be given intravenously daily, for three to five days.

3) Abdominal paracentesis has proven successful at times.

4) Nitrogen Mustard 0.1 mg. per kilogram per day diluted and given intravenously has been tried, but generally is less effective and more toxic than the other means listed. We have not employed Nitrogen Mustard.

Probably, the least common forms of renal diseases encountered in children are subacute and chronic glomerulonephritis. The clinical manifestations are variable. They usually resemble children with the Nephrotic Syndrome. Occasionally they present themselves with the syndrome of chronic renal failure. Failure to thrive, anemia, proneness to infections, chronic acidosis, headache, vomiting, and severe bleeding episodes are some of the usual manifestations. Laboratory studies will often reveal:

1) Poor kidney function by the inability to concentrate, as well as marked depression of other tests of kidney. function.

2) Persistent renal azotemia.

3) Persistent hypertension.

4) Severe anemia.

5) Hyperkalemia, and/or hyperphosphatemia are sometimes noted but are usually encountered terminally.

Despite the poor eventual prognosis, much can be done to improve the status of these patients. Some of the measures recommended are:

1) A diet rich in carbohydrate and fat, for its protein-sparing effect.

2) One must determine the optimal

amounts of sodium and potassium in dietary intake needed by these patients in order to maintain homeostasis.

3) The diet should also be rich in calcium and low in phosphorus, particlarly if the patient tends to retain phosphorus.

4) Amphogel® or Gelusil® can also be employed before meals to decrease the absorption of phosphates.

5) Blood transfusions, if necessary, should be used to reduce the symptoms of severe persistent anemia, and

6) Prophylactic antibiotics are generally useful in cutting down the number of intercurrent infections. One may thus eliminate many of the renal exacerbations which would otherwise occur.

Finally, Acute and Chronic Pyelonephritis occur with sufficient frequency to warrant discussion here. It is important to emphasize that Pyelonephritis can, and indeed often does, clinically resemble the other three major types of medical renal disease. It is axiomatic that one attack of Pyelonephritis in a male child requires a detailed renal work-up. We believe that a female child, because of her anatomy, is entitled to one such attack. More than one bout of Pyelonephritis, however, also demands the same detailed renal study. Many cases of Acute or Chronic Pyelonephritis are intimately associated with genito-urinary obstructions resulting from congenital malformations. Pyelonephritis can become clinically apparent in the following ways: 1) It can mimic medical renal diseases; 2) It can manifest itself with a typical attack as one sees in adults, with flank or abdominal pain, with chills and fever, with pain that radiates into the groin and with such urinary symptoms as dysuria, frequency, burning, etc. 3) It frequently can be very silent and only manifest itself with such subtle symptoms as failure to thrive, persistent anemia, and fever of undetermined origin. It is probably unnecessary to state that Pyelonephritis can slowly, but progressively, destroy the renal parenchyma. Early recognition is extremely important. Adequate treatment therefore includes:

1) Early Diagnosis.

2) Identifying the infecting organism by culture, and since most of these are gram negative, require

3) Sensitivity studies, so that the proper antibiotics, and/or chemotherapeutic agents can be used, and

4) Correction of any underlying congenital obstructive anomaly.

In conclusion, we have seen that the physician can do a great deal to promote the recovery of the child who is afflicted with acute renal disease and can do much to promote the well-being of the child who is unfortunate enough to have chronic renal disease. As in almost every other field of Medicine, optimal management depends on accurate diagnosis.

PRESENT STATUS OF PULMONARY RESECTION FOR METASTATIC MALIGNANCIES

WILLIAM H. KAUFMAN, M.D.*

Two factors have converged in the recent past to give rise to a new concept in the treatment of certain patiens afflicted with malignancies. First, has been an increasingly aggressive approach to the detection and treatment of cancer in general; and second, has been the marked development of thoracic surgery in the past two decades. It was, therefore, inevitable that when some patients presented themselves with a solitary pulmonary mass, which appeared after an apparently otherwise complete eradication of the primary tumor, with no evidence of other metastasis, and in good general condition, the temptation was great to resect the mass in the hope, that by so doing, the patient might be permanently cured of his tumor.

The first tentative experiences along this line formed a clinical experiment, the results of which have been encouraging enough so that the practice has spread, and increasing numbers of cases are being added to the literature. The present effort is an attempt to review and assess the literature on this subject, to derive whatever clinical lessons have been learned by this experience, and to help disseminate this information.

Although lung resection for tumors goes back to 1855, this was for direct extension of tumors through the chest wall. The first proven case of lung resection for a metastatic lesion seems to have been in 1927 for a slow growing fibrosarcoma of the breast. It is interesting that this patient had undergone 10 operations in 35 years for various recurrences of this tumor and apparently did well subsequently. Since that time, many single and multiple case reports have appeared in the literature until these now total 91.

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The largest series from a single institution has been presented by Hood, *et al.*, from the Mayo Clinic. There are 43 cases in this series. Strieder has presented the experience with 22 resections on 20 patients at the Boston University School of Medicine, and Kelly and Langston have added 18 cases from Hines Veterans Administration Hospital. Thus there are available in the surgical literature the results of 152 instances where this procedure has been applied.

However, as will be seen, this number is very small when dealing with a disease as complex as cancer. In addition, many of the survivors have not been followed long enough to establish their ultimate course. However, the series seems large enough to establish some tentative conclusions.

Minor did an interesting study pertaining to this problem in 1950. (Chart 1.) He gathered the records of all the patients at the University of Michigan Hospitals in a five-year period who had lung metastasis from 1937-1947 and tried to determine the natural history of the group. The total number of cases with carcinoma was 5,727. Of these, 314 had pulmonary metastases visible in radiological examination. Actually, this figure is probably higher because some metastatic lesions are too small to be seen on X-ray, and also due to the fact that some would be expected to appear after the films were taken.

Of the 314 cases, most, or 79%, were clearly unresectable because of the presence of extensive diffuse disease. Of the 69 patients remaining, with a localized pulmonary shadow, 55 were unresectable because of an uncontrolled primary site of the tumor, metastasis to bone, liver or other sites, or invasion of vital structures. This left only 14 patients out of the total group who were suitable candidates for the procedure under discussion.

That is, they had a solitary lung mass, no other metastases to bone or elsewhere, and no evidence of persistence of tumor at the primary site. These 14 cases were then followed and 11 later developed recurrence, either local or distant, so that of the 14 candidates only 3 could be expected to become long term survivors, or roughly a salvage rate of 20% of suitable candidates. This would be the maximum theoretical figure on the basis of this series.

It is interesting that this does agree fairly closely with the actual clinical experience. In the Michigan series, 2 of these patients were operated upon and survived 4 and 7 years. Both were sarcomas. One can also see from these figures that this modality of therapy is only open to a small portion of the entire patient population with carcinoma.

In considering any surgical procedure, of course, one must always weigh the potential benefits against the possible morbidity and mortality. The aim of the physician is to prolong life and relieve suffering and he does neither if his mode of therapy kills the patient or adds to his burden for a significant percentage of his remaining life span. Actually, however, the mortality figures do not seem to create an issue. Thus, of the 43 cases in the Mayo Clinic Series, there was only 1 operative death and this in a pneumonectomy. There was only 1 operative death in the Boston University series, due to a transfusion reaction. There was no operative mortality in the Hines Series.

In dealing with a disease which itself carries a 100% mortality, obviously this degree of operative mortality seems insignificant. As regards morbidity, certainly a thoracotomy is a major procedure and results in a short, but definite painful and disabled state for the patient. It has been demonstrated, as will be shown, that 75% of patients live at least a year following thoracotomy, so that only a tiny percentage of the time remaining to even those who ultimately succumb to their cancer, is consumed by their surgical experience. This seems a small price to pay for the potential benefits of the procedure. In this connection, it is well to note that conservative procedures such as lobectomy, segmental or wedge resections are preferred to pneumonectomy, when dealing with metastatic lesions, and these procedures are much better tolerated.

The long term survival figures are difficult to assess at the present time, because of the small number of cases that have been followed sufficiently (5 or more years), plus the variability of the disease. Thus, in the Mayo Series, there were only 11 cases followed 5 or more years, but 3 of these survived, giving a 5 year survival rate of 27%. Eighteen patients were followed for 3 or more years and 6 or 33% of these survived. Out of 41 followed for 1 year, however, 30 or 73% were alive. It will be interesting to see the results when this rather large group has been followed for a longer period of time.

Of the 20 cases from Boston, 15 or 75% were alive at the end of one year. Four patients survived for more than 5 years although one had residual disease. Although this is a small series, a respectable 5 year survival rate is again demonstrated. Of 82 instances, followed for 2 years or longer, in the literature, including the Hines Series, 19 or 23% have lived at least 2 years.

In summary, one may state that the short term survival figures are excellent, but the long term statistics, while promising, are not adequate at the present time to form statistically valid conclusions.

In addition to the possibility of long term survival or even "cure" offered to the patient with cancer by the resection, there is an additional reason to consider thoracotomy. That is, the very real possibility that a localized shadow in the lung fields may not be a metastasis at all, but a second primary bronchogenic carcinoma or even a benign lesion, such as a granuloma, adenoma, hamartoma, etc. It seems to be well established that patients with carcinoma are more susceptible to the development of a second carcinoma than the normal popula-

tion. Thus, on a basis of 2,000 autopsies, Warren and Gates feel that 2.4% of carcinoma patients will have multiple primaries.

In the Memorial Hospital Series of 1473 lung tumors, 1.6% also had primary carcinoma in other organs. The experience of the Hines group is notable in this respect. Of 22 thoracotomies for supposed metastatic disease, they found that 4 patients or 18% actually had second bronchogenic primaries of which 3 were resectable. They properly point out that there is no clinical method of distinguishing a metastatic lesion from a second primary, short of exploratory thoracotomy and biopsy.

This experience was shared by the Boston Group to an almost identical degree. They also found 4 of 20 lung masses to be unrelated to the primary lesion. Three of these proved to be benign at thoracotomy. Therefore, it is clear that the clinician faced with a patient with a known carcinoma which has been apparently controlled, a lung shadow may not mean a metastasis, but rather a new primary in the lung or even a benign lesion.

A third possible benefit of resectional therapy of solitary metastatic nodules is that of palliation. Admittedly, this is a difficult matter to quantitate, and much will depend on the individual clinical situation. However, it is stated that from 50-70% will have symptoms of varying intensity from the intrathoracic mass. These include cough, dyspnea, persistent sputum, pleuritic pain, and hemoptysis. Occasionally, the symptoms themselves are severe and disabling in which case relief by resection can be quite gratifying. In other cases, the psychological effect of removing a source of annoying symptoms that constantly remind the afflicted individual of the presence of a malignant lesion in his chest, is not to be dismissed lightly.

In any event, the presence or absence of symptoms has no prognostic value in selection of patients for surgery. Among the published studies, the symptomatic or asymptomatic yield about the same percentage of long and short term survivors.

The factors that seem to influence prognosis are not clear at the present time, owing to the paucity of published material. However, in most series sarcomas seem to yield more survivors in proportion to their relative prevalence. In other words, most series seem to have more survivors in the operated and surviving groups than should be expected considering the normal preponderance of carcinoma over sarcoma. This seems to indicate that localized accessible metastases occur more frequently in sarcoma and that they have a somewhat more favorable prognosis.

However, many long term survivals are recorded for carcinoma and in the Mayo Series carcinoma survivals led those of sarcoma at 1 year — 80% to 54.5%. Tumor type, therefore, cannot be used as a criterion for selection of cases. Long term survivals have been recorded for the following types of tumors: Hypernephroma, adenocarcinoma of rectum, bowel, ovary, breast, teratoma of testes, and chorioepithelioma.

On the basis of very sketchy information so far, a few hints of trends may be discerned. The size of the lesion upon X-ray, seems to influence prognosis. The smaller lesions have better results at one year (75%) than large (50%) in the Mayo Series. The length of time between original treatment of the primary and the appearance of the metastatic deposit, seems to have some prognostic import. Lesions which appear after 3 years, yield a one year survival of 89% vs. 52% for those that appear in less than 3 years. This might be expected from differences in biologic growth potential of different neoplasms.

There seems to be agreement in the literature that the extent of resection to be done for solitary metastasis is logically a limited one — that is, it should be a lobectomy, segmental or wedge resection, rather than a pneumonectomy. Pneumonectomy should be reserved for the occasional case where the mass is so located that lesser procedures are technically impossible.

Most authors feel that tumor emboli from metastatic lung lesions are less like-

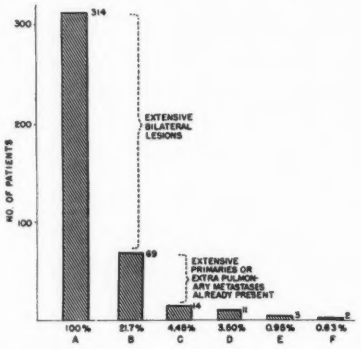
ly to travel along the lymphatics than those of primary bronchogenic carcinoma. However, on the basis of several cases where mediastinal nodes were involved, it is believed by Ehrenhaft that metastatic lung lesions do travel along lymphatic pathways to the mediastinum. The possibility that the metastatic lung mass may "seed" by hematogenous spread as well as local extension, forms the basis for the rationale of its resection. A limited resection is as effective in this respect as a more extensive one.

This can be accomplished with a very low mortality rate which should be less than 2%. The morbidity involved is minimal.

The type of tumor, its size or time of appearance, are not reliable criteria to use at the present time in the decision for or against thoracotomy.

In the light of present information, the extent of reaction should be limited to lobectomy, segmental or wedge resection, depending on the exact anatomical site involved, rather than pneumonectomy unless technical considerations dictate otherwise.

FATE OF PATIENTS WITH METASTATIC PULMONARY NEOPLASMS*



(A) Total number of pulmonary metastases. (B) Pulmonary resection anatomically feasible. (C) Primary apparently controlled. (D) Later development of extra-pulmonary metastases or recurrence of primary. (E) Fate unknown. (F) Pulmonary resection carried out.

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SUMMARY

In summary, it seems to be well established that resection of solitary lesions in the lung in patients whose primary malignancy is controlled, who do not have extrapulmonary metastasis, and who are in good general condition, is justified at the present time. Such a policy can be expected to result in the following advantages:

a. The detection and treatment of a certain number of new primary lesions.

b. The occasional discovery that a presumed metastasis is in reality a benign lesion.

c. A respectable number of long term survivals.

d. A varying, but frequently gratifying degree of palliation to the remainder.

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DRUG ALLERGY

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Drug Allergy is a subject which has gained momentum in recent years due to the introduction of many newer agents employed in the treatment of disease. The subject has long been known to physicians, but owing to the addition of sera, sulfonamides, penicillin, steroids and other pharmacologic preparations to our therapeutic armamentarium, we have become more cognizant of peculiar reactions which we term "allergic."

The term "allergy" usually refers to an altered physiologic response of tissues to certain physical or chemical stimuli. Basically, it is believed, in the light of our presently accepted theory, that all such reactions are based upon allergen-reagin interreaction, with the release of a toxic substance, often referred to as an "H" substance, or histamine, which in turn, is responsible for the pathologic physiology which then ensues. It would be nice if drug allergy followed this pattern, but, unfortunately, it does not do so. In order for an allergic reaction to occur following contact with drugs, there must be produced one or more of the commonly accepted syndromes which are known hypersensitivity reactions. These include: asthma, urticaria, angioedema, rhinitis, gastrointestinal disturbances, anaphylactic shock, and a number of others. To further complicate the picture, reactions to drugs may occur in certain persons, without creating a typical allergic reaction, yet creating an abnormal pharmacologic response, or toxic effect. To this type of reaction we give the name "idiosyncrasy" or "drug intolerance." Examples of this type may be found in persons taking quinine, who develop severe tinnitus, vertigo, and vomiting after ingesting a normal pharmacologic dose. Similarly, there are many who develop sialorrhea, nausea, and vomiting within fifteen or twenty minutes after ingesting a five grain tablet of acetylsalicylic acid. Since there is no typical allergic syndrome produced by such reactivity, we are inclined to term it an idiosyncrasy.

The present concept of allergy to drugs would appear to be based on a firm union between the drug, even of low molecular weight, with some blood protein, probably a globulin, to form a perfect antigen. The low molecular weight drug is incapable of producing its own reagins or antibodies, but when combined as above, it can do so. Once formed, such antibodies will react to subsequent introductions of the original simple chemical or to closely allied substances. This haptene-like reaction seems best to explain the failure of most drugs to respond to direct skin testing procedures and for the absence of circulating antibodies as shown by Prausnitz-Kustner passive transfer method.

The frequency of occurrence of drug allergy has been variably quoted by different authors. Abromovitz reports one patient out of sixty-five as compared with one in two thousand published by Sutton. The marked variations depend, of course, on whether the author is in general practice or in the field of dermatology or allergy. Frankly, we would be hard-pressed to offer a percentile figure of the frequency of drug allergy as seen in our practice. Suffice it to say that such reactions are not infrequent in any Allergist's office. It has been postulated that certain predisposing factors seem to play a role in causing drug allergy to develop. These include: imbalance of the physiologic states, as at puberty or menses; intercurrent infections; diseases of the liver, kidneys, or adrenal glands; other allergic manifestations; physical

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factors due to barometric changes, heat, cold, sunlight; emotional disturbances; mild deficiencies in minerals, electrolytes, vitamins, and glands of internal secretion; and finally, certain underlying dermatologic conditions, such as acne, chronic furunculosis, atopic dermatitides, and seborrheic dermatitis. Sulzberger and Baer have shown that certain people with basic skin lesions, as mentioned above, are more susceptible to particular drugs. The atopic seems to react more often to salicylates, while those with a history of past or present epidermophyton infections have a much higher incidence of penicilin hypersensitivity. Surely the acne patient developing an allergic response to iodides has been seen by many. A summary of Sulzberger's classic description of drug eruptions states the known facts clearly: even minute amounts of a drug, well tolerated for weeks, months or years, may suddenly produce severe reactions; when such an eruption has occurred, it is likely to recur upon subsequent minute exposure to the offending drug, or to a related drug; the cutaneous response is generally different from that produced by the pharmacological action of the drug; some drugs with entirely different pharmacologic actions often produce identical eruptions, and the same drug is often capable of producing radically different manifestations in different individuals, or in the same individual at different times; the amount required to elicit eruptions is often smaller than that necessary to produce pharmacologic or toxic effects.

Sensitization to drugs may develop after ingestion, injection, contact with mucus membranes, topical application, or by inunction. Reactions producing a definitely accepted atopic response, viz., asthma, urticaria, angioedema, etc., are considered true drug allergy; whereas, those which produce other type reactions are usually idiosyncracies, intolerance, or toxic reactions. The diagnosis is based mainly on awareness of such conditions by the physician, a clear, concise history by the patient, past history, especially with reference to previous or other allergic illness, and a positive family history of allergic disease which may be found in about seventy percent of all patients seen. The avoidance and reexposure test may be used. Attempts to perform skin tests using the suspected drug usually fail. There have been published reports indicating occasional positive reactions, as with penicillin. Some investigators have shown that mixing the simple chemical with the patient's blood has yielded occasionally positive results. This has, however, not been consistently confirmed. Others have used the serum of patients on high dosages of sulfonamides, with high blood levels, for testing purposes, but uniformly successful reactions have not been seen.

Specific Drugs and Their Reactions

The most common drug incriminated in this form of hypersensitivity reaction is aspirin. Bronchial asthma, urticaria, angioedema, fixed drug eruption, migraine, pruritis ani, and various gastrointestinal manifestations are frequently associated. Van Leeuwen reports that ten per-cent of all asthmatics are aspirin sensitive. Such patients are often also sensitive to other drugs, such as phenobarbital, aminopyrine, antipyrine, and sodium salicylate. Skin tests are negative. Deaths caused by the development of asthma following aspirin ingestion are probably not rare. Prickman and Buchstein analyzed sixty-two such patients and found that all but one had a positive personal or family history. They report respiratory reactions most common, with gastro-intestinal symptoms next in order.

Aminopyrine usually produces asthma. Some believe that granulocytopenia, often shown due to this drug, may be on an allergic basis.

Quinine may cause coryza, edema of the uvula, thrombocytopenic purpura, in addition to shock and numerous skin eruptions. Occasional positive skin tests have been reported.

Morphine, codeine and their derivatives are known as urticariogenic drugs, and can produce skin reactions in everyone. Shock, vomiting, and numerous skin reactions are the usual forms of allergic response.

Barbiturate allergy is quite common.

Cutaneous morbilliform eruptions, bronchial asthma, rhinitis, urticaria, fixed drug eruptions, blood changes, or anaphylactoid reactions are often seen.

Sulfonamides have caused reactions in two to fifteen percent of all patients using this drug or one of its many derivatives. Various dermatitides, fever, asthma, urticaria, and angioedema have been encountered.

Reactions often seen, are: *eczema,* caused by arsenicals, chloral hydrate, ephedrine, mercurials, quinine, and salicylates.

Erythemas have often been reported as due to antipyrine, arsenic, aspirin and barbiturates.

Morbilliform, scarlatiniform, pityriasis-like lesions, bullous, erysipeloid, urticaria, angioedema, erythema exudativum multiforme, erythema nodosum, exfoliative dermatitis and fixed drug eruptions are only some of the varities of the many dermatologic reactions frequently seen. Actually almost any medication may be responsible for the causation of drug allergy.

Injectables are often a factor in the development of allergic responses. Of all the hypersensitivity reactions seen, serum sickness is undoubedly the most frequently encountered. The reactions are either a true serum sickness disease, or an immediate reaction. Typically, serum sickness usually occurs seven to ten days after an injection of preparations made with horse or other sera. Occasional delay in onset of such reactions may occur up to thirty or even sixty days in rare instances. Characteristically, fever, urticaria, inflammation of smaller joints of the hands and feet, intense itching, and lymphadenopathy often accompany true, severe serum sickness disease. Immediate serum reactions, manifest by anaphylactic shock or atopic reactions are seen too often. Suffusion of the face, generalized urticaria together with angioedema, rhinitis and asthma are often associated.

Precautions before the administration of any serum preparations should be exercised by all physicians. Careful history of previous serum injections, or of any other allergic illness in the patient or in his family should be noted. Scratch and intradermal tests will yield positive results in sensitive individuals.

Transfusion reactions are frequently encountered, even in the most careful hands. One of us (Frankel, et al.) has shown that the addition of injectable chlortrimeton to blood used in transfusions, will greatly reduce reactivity.

Insulin reactions are not uncommon. They may include local irritation with edema or an arthus-like response, urticaria, angioedema, shock with associated reduction in blood pressure, nausea, vertigo, diarrhea, abortion, purpura, and rhinitis. Positive skin tests may be obtained by scratch and intradermal procedures. The lack of proper insulin responses in severe diabetics has often been attributed to insulin drug allergy. The serious importance of this drug in juvenile and severe adult diabetics may readily be understandable by all, and the need for help, as well. Often changing from beef to hog or other insulin derivatives will be sufficient. Globin, zinc, or other combined insulin products may be substituted. However, if the pure crystalline insulin is the proved cause, trouble ensues. Rapid, multi-daily hyposensitization injections, starting with very dilute extracts and increasing in concentrations as rapidly as the patient's condition permits will often help reverse the condition. The use of combined injections with antihistamines may also aid in such persons.

Liver allergy, similar to insulin reactions, is frequently encountered. In such persons, hyposensitization may help, although substitution therapy is available.

Other injectables frequently responsible for allergic reactions are: hormones, vitamins, pancreatic extracts, estrogenic substances, arsphenamines, mercurials, bismuth salts, barbiturates, gold salts, and many others.

Insect bites and stings often cause marked local reactions with evidence of toxicity or hypersensitivity phenomena,

including shock-like responses. Bees, wasps, mosquitoes, fleas, lice, bed bugs, chiggers, or snake venom may be responsible.

Treatment, in general, for all drug reactions of allergic types, consists in accuracy of diagnosis, avoidance, use of antihistaminics before, during, and after the use of needed drugs, local preparations as for skin eruptions, and the use of the steroids in the more severe forms of this disease entity.

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CLINICOPATHOLOGIC CONFERENCE

Presented at Mount Sinai Hospital, Chicago, Illinois

DR. B. PEARLMAN, Chairman **DR. H. RAPPAPORT, Secretary**

CLINICAL HISTORY

The patient, a twenty year old white male X-ray technician, was admitted to the hospital on September 6, 1956 because of an elevated temperature, enlarged cervical lymph glands, nausea, icterus and dark colored urine. Three weeks prior to this admission, the patient developed a low-grade fever ranging between 99° and 100° which subsided on Panmycin®. The patient was told that his throat was inflamed and apparently there were no abnormal findings, but eight days later he noticed enlarged cervical lymph glands and the return of the temperature. Two days later, the patient noticed that his urine became darker in color while the stool became lighter. At the same time a moderate degree of icterus of the sclerae was noted.

Past and Family Histories: The patient was allergic to penicillin and had received the first two doses of polio vaccine two months prior to admission.

Physical Examination: revealed a normally developed male who appeared to be in no acute distress. The temperature was 99.4°. The blood pressure was 140/85 and pulse 76. The skin and sclerae were slightly icteric. Enlarged and tender lymph nodes were palpated in the cervical and axillary regions bilaterally. The lungs were clear to percussion and auscultation. The heart was within limits of normal on percussion. No masses or organs were palpated in the abdomen. The extremities were free of edema. Neurological examination was essentially negative.

Hospital Course and Treatment: On the day following admission to the hospital, the patient's temperature went up to 101.6° and he complained of nausea, which was only partially relieved by Dramamine®. The patient appeared to be somewhat drowsy but oriented and responded to verbal stimuli. An episode of hematemesis was recorded during the third hospital day. On the fourth hospital day, while in the washroom, he had an episode of syncope, following which he became disoriented and semicomatose and incontinent of feces. The blood pressure dropped to 100/70. A medical consultant who was called in noticed diffuse petechiae on the lips, mouth, body and extremities. The spleen appeared to be enlarged to percussion and questionably palpable. A spinal puncture gave clear fluid, 220mm. water pressure, and no evidence of any block. During the following night the blood pressure remained low, ranging from 100 to 80 (systolic), and temperature continued to be elevated. Because of the presence of diffuse petechiae and the possibility of septicemia (meningococcus), isolation technic was instituted. 500cc. of whole blood was given followed by 1000 cc. of 5% glucose in saline with Cortisone, 100 mg., and Erythromycin—500mg. On the 5th hospital day the patient became very restless, stuporous and violent at times. Sodium luminal intravenously was of no help. A moderate degree of sedation and hypnosis was obtained with Paraldehyde I.M. in doses of 4 cc. which had to be repeated every two to three hours. The patient was perspiring profusely; his respiration was rapid with temperature ranging from 100° to 103° rectally. Short episodes of convulsions, involving the upper extremities, were noted. Blood, rich in platelets, and steroids I.V. and I.M. were given. Erythromycin was added to the intravenous fluids. Emergency splenectomy was considered, but not feasible in view of the patient's poor condition. One X-ray treatment to the spleen was given. Extreme restlessness persisted, and on the seventh hospital day, after a short episode of muscular twitching involving both upper extremities, the patient expired.

LABORATORY DATA

Bl Cts:	RBC	Hgb.	C.I.	WBC	Stabs	Segs	Eos	Lymphs	Mono	Bas	Platelets
9/7/56	3.9	12.4 (80%)	1.02	5,550	3	58	3	29	7		
9/8/56	3.4	10.7		5,000							
9/8/56	2.6	7.1	0.84	9,250	20	44	1	20	8	1	decreased
"	Meta-4; Myelo-1										
	Morphology: anisocytosis 3-4; poikilocytosis 1+; nucleated RBC 4/100; spherocytes 1+; blast and toxic granulations 1										
9/12/56	3.3	10.2	0.98	6,510	22	45		20	7		
"	Meta-5; Myelo-1										

Platelet counts: 9/10/56: 33,000. (Bleeding time-15 min; clotting-6 min. No clot retraction in 24/hrs).
9/11/56: 41,000
9/12/56: 40,000

Prothrombin time: 9/7/56: 15 - 14 85%.

Fibrinogen: 9/10/56 - 0.15 gm%.

RBC fragility test: 9/11/56: PATIENT beginning hemolysis at 0.57%; complete 0.21%.
CONTROL beginning hemolysis at 0.42%; complete 0.30%

Heterophilic antibody test: 9/7/56: negative.

Chemistry:	Serum prot.	Alb.	Glob.	A/G	Bili.	T/D	Choles.	est.	Thym.	Alk. phos.
9/8/56	5.8	2.9	2.9	1.0	3.5/0.3		166	68%	2.4	2.6

Ceph. Chol.	Transaminase	Glucose	BUN	Creatin.
2+	126 units/ml.	128	45	1.5

9/10/56	Serum Chl.	Sod.	Potassium
	95	135	3.9

Urinalysis: 9/7/56: 24 hr. urine for urobilinogen - 4.3 units.
9/12/56: 24 hr. urine for urobilinogen - 0.3 units.
Repeated urinalysis showed persistently 3+ to 4+ proteinuria, numerous RBC and WBC, casts, and on one occasion, free Hgb. (9/12/56)

Bacteriology: 9/10/56: Gram stain of petechial material negative for microorganisms. Blood culture - negative. Peripheral blood negative for L. E. Cells (1 specimen).

Serology: 9/10/56: Agglutination tests for typhoid, para-typhoid, brucellosis, Weil-Felix were all negative.

9/10/56: Cold agglutine test: negative.

9/12/56: CRP - 3+ ASO - 12 units.

Routine Feces Examination: 9/9/56: Stool - 4+ for occult blood, negative for parasites.

9/10/56: Direct Coombs test - + very weak.

Bone Marrow: (9/10/56) "Marked erythroid hyperplasia of the normoblastic type. Megakaryocytes are present in adequate number. Only a few of them show platelet formation, and some are atypical and immature".

Dr. A. Cohan*: I first saw the patient when he was 13 years old. There was a history of having been treated as a youngster for a Frohlich's syndrome, with injections. The last injection was about 3 or 4 years prior to when I had seen him, in other words, at the age of 10. When I examined him he had enlarged breasts, a small penis, the testicles were descended, he had fat distribution around the hips, arms and thighs, and

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there was no pubic or axillary hair. The remainder of the visits when I had seen him were for upper respiratory infections and for thrombosed hemorrhoids. One interesting point was that while he gave a history of having been allergic to penicillin, I do not have that information on my record and I always ask for allergy. In 1951 he received penicillin for celluitis of the toe, and in 1952 he received penicillin for a sore throat, with no apparent complications. The last time I saw him in the office was in October, 1953 with an internal derangement of the knee. He was somewhat of an athlete at that time. Incidentally, he grew up to be a perfectly normal looking male, he did not look like a Frohlich; as a matter of fact he was to be married six weeks after I hospitalized him.

I told the family at the time I had seen him for the so-called upper respiratory infection, that in view of the temperature and the enlarged lymph nodes, the only thing I could consider was infectious mononucleosis, and that this in itself was a benign condition and the only complication I was looking for was a hepatitis with some jaundice. Lo and behold, a few days later they called me and said they thought he was jaundiced. I went to see him and he was jaundiced, and that is when I admitted him to the hospital as an infectious hepatitis secondary to infectious mononucleosis. He was in the hospital seven days, with a rapid fulminant type of disease. He was admitted on September 6; on the evening of the 9th I received a call that he had fainted in the washroom and became disoriented. That was about 11:00 P.M. and I went to see him. I was able at that time to see that there were petechiae present; the day before and that morning neither the consultant nor I had noticed any petechiae. We considered at that time that we had some type of hemolytic affair. We considered and ruled out leukemia, bacterial septicemias, Weil's disease, endocarditis, etc.

On September 10 we got the report about the platelets being decreased, and my impression then was a combination of one of the hemolytic anemias with a thrombocytopenic purpura. I was not in a position at the moment to make a definitive diagnosis.

Dr. L. Cardon:* I would like to point out three possible factors which may make for discussion by Dr. Davidsohn. In the first place, this man was an X-ray technician, for a year before admission. We even called the man he worked for and he assured us that there was no possibility of over exposure to X-ray. In the second place, you heard the story that he was allergic to penicillin, just in what way we did not know. The third point that should be made, not that I know the significance of it, is that four weeks before admission he received a polio vaccination. I think in the discussion you will probably become aware that these things have been discussed and commented upon in the literature in a sort of an off-hand way, because nobody knows the significance of these things.

As far as what we saw when I saw this boy at 12:00 midnight on September 9, as Dr. Cohan mentioned there were numerous petechiae, which apparently had not been present before; he had delirium, fever and a spleen which seemed to be enlarged to percussion. The first thing we had to do from the standpoint of the surroundings in the hospital was to exclude a meningococcemia and other types of sepsis—streptococcus, staphylococcus, acute septicemia and acute or subacute bacterial endocarditis. I don't think we had a complete count yet—the question was did he have an acute leukemia? We did know, even at that time, that this man had a hemolytic anemia, because he was jaundiced but he had an acholuric urine; he had an elevated serum bilirubin but the direct bilirubin was low, so that the total bilirubin was elevated because of the indirect bilirubin, which indicated hemolysis. Subsequently we found that there was a slight increase in the urinary urobilin, so there was no question even that night that he had a hemolytic anemia together with the septic picture and the delirium. Also, he had a thrombocytopenic purpura, which we suspected

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from the petechiae; this was rapidly confirmed by a count, and the smear showed the platelets to be diminished.

The statement was made even that first night if the condition was not infectious or leukemic, then the combination of fever, petechiae, hemolytic anemia, thrombocytopenic purpura, severe nervous symptoms, and an apparently rapidly progressive downhill course, speaks strongly for a thrombotic thrombocytopenic purpura. If that were the diagnosis, it would not affect the condition one way or another, but again, we had to go to great lengths to exclude a meningococcemia, so I suggested that the petechiae be punctured and that direct gram smears be made for gram-negative intracellular diplococci, which were not found. Subsequently the blood cultures were repeatedly negative. This question of the possibility of a meningococcemia or a Waterhouse-Friderichsen syndrome became more acute, because early in the morning his blood pressure went down to 80 systolic and his pulse became dicrotic. As long as this diagnosis could not be immediately disproved, we instituted isolation technic and started therapy with intravenous Cortisone and Erythromycin, as you heard. We did not use the sulfa drugs. Even in this day of antibiotics, as far as the therapy of meningococcemia is concerned the sulfa drugs are best, but in the presence of a hemolytic anemia and a thrombocytopenic purpura, I was not brave enough to institute sulfa therapy, particularly since we did not know for sure that the patient had meningococcemia.

The question of the etiology will be discussed, and I believe we mentioned that the subject of hypersensitivity had been considered in the literature. I will not go into the pathology. I might say that the question of infectious mononucleosis with symptomatic acute hemolytic anemia and thrombocytopenic purpura was certainly not excluded the first night. The question of acute disseminated lupus erythematosus was not excluded, and the question of rickettsial disease was also considered because of the petechial eruptions. As a matter of fact, I think we had the urine examined for leptospirosis because this situation might arise in that condition.

As far as the actual therapy is concerned, when it became apparent, after repeated negative blood cultures and the negative smears from the petechiae, that we were not dealing with a septicemia, and when the marrow examination showed that we were not dealing with a leukemia, it became more and more obvious that the original diagnosis of a thrombotic thrombocytopenic purpura, which has also been called a thrombohemolytic thrombocytopenic purpura, was correct. This is a highly fatal disease, nevertheless we could not sit back with folded arms, and we continued to use the steroids, which have been recommended—the number of cases reported is not large enough to fully evaluate any type of therapy. The only case I think which was reported as having lived for 3 years was a case in which a splenectomy was done. On the other hand, in many cases in which splenectomy was done, the patient expired without any apparent effect of the splenectomy on the disease. Again, I did not have the courage to recommend, in a boy as acutely ill as he was, an emergency splenectomy, particularly since its value has not been proved, and the consensus of opinion, at least until that time, seems to have been that it is not effective. However, I saw no objection to giving X-ray exposure to the spleen, although I knew that would take some time to become effective.

Dr. I. A. Friedman:* We have seen several patients with this interesting disease. Perhaps the most dramatic and interesting example of a clinical remission was a young female patient who presented as a classical thrombohemolytic thrombocytopenic purpura with severe neurological findings, hemolysis, and thrombopenia. During a stage in her illness which was not as desperate as that of the patient discussed here, splenectomy was performed, and there resulted a complete remission persisting as of two years after the initial episode. The case that Dr. Cardon referred to is very inter-

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esting; that is, a patient who presented with a hemolytic episode relieved by splenectomy three years before the full-blown symptoms of this disease had manifested themselves. Therefore several cases, including the patients mentioned by Dr. Cardon and myself, have survived after splenectomy. However, most of the cases that have had splenectomies during the fulminant stage have not done well. I know of two such cases: one was a young man with transient neurological findings who developed severe thrombopenia and hemolysis and expired despite steroid therapy and splenectomy; the second was a young woman who had a splenectomy during the desperate stage of her illness. We might postulate that splenectomy may be more beneficial during the less fulminant phase of the disease.

Another unusual facet of this case is the presence of a positive Coombs test. This is unusual in thrombohemolytic thrombocytopenic purpura, even though a case with a positive Coombs test was recently reported in the literature.

There has also been much written and discussed about the relationship between this disease and the hypersensitivity group or diseases, especially lupus erythematosus. It is most interesting that the patient I described as being alive two years after successful splendectomy developed a positive L. E. test seven months after the splenectomy. At no time did she develop any signs and symptoms of disseminated lupus erythematosus.

Dr. I. Davidsohn:* First a few words about the clinical-pathologic findings. This patient had thrombocytopenia and anemia, which is possibly on an autoimmune basis, because he had a weakly positive direct Coombs test. I am not too sure that one can attach too much importance to such a weakly positive Coombs test. On the other hand it has been pointed out that some of the blood findings in these patients are intermittent. For example, considerable variation in the number of spherocytes may be present. Consequently there may also be variations in the positive Coombs test. Hence the Coombs test may have been positive if repeated. A low white count was present on a few occasions. I reviewed the blood counts and found that we did more than those recorded here, and on two occasions the count was about 5,000. It may not be without significance that there was a moderate shift to the left with an increase of stab cells, ranging from about 12 to 23. Another point of interest: the patient had 4 nucleated red cells when 100 white cells were counted. Actually, when the last three blood smears were re-examined there were 56 nucleated red cells/100 white cells, which is an impressive increase, especially in view of the moderate anemia. The patient received three transfusions of whole blood on the 9th, and two on the 10th. After the transfusions the blood count rose from 2.5 million to 3.3 million. To sum up the laboratory findings we have a suggestion of a pancytopenic manifestation, a shift to the left in the differential count, an outpouring of nucleated red blood cells, and an increased fragility of erythrocytes. The urine showed red cells.

It has been pointed out in the literature that there is an intermittent spherocytosis which varies from day to day. That, together with red cell survival studies, suggest that there may be an autoimmune element in the anemia. In addition to the positive Coombs test in the case mentioned by Dr. Friedman there have been several others reported in the literature, for example, a recent one in the Annals of Internal Medicine, where the Coombs test was strongly positive. It seems that there are autoimmune aspects in this disease, at least as regards red cells. A little later I will point out a similar autoimmune mechanism with regard to platelets.

The bone marrow preparation obtained during life showed a normoblastic hyperplasia, as would be expected in a case of hemolytic anemia. The megakaryocytes were more numerous as is frequently the case in thrombocytopenia. More interest-

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ing was the qualitative change in the megakaryocytes. Some showed a deep basophilia, and an inhibition of platelet formation. This could be interpreted as evidence of immaturity of the megakaryocytes.

Autopsy findings:

FINAL ANATOMIC DIAGNOSIS

Cardiovascular system. Heart: Myocardium: hypertrophy; arteriolocapillary thrombosis of so-called "platelet thrombosis type".

Lymph nodes: Focal necrosis.

Spleen: Splenomegaly (430 Gm.).

Bone marrow: Megakaryocytic hyperplasia and immaturity.

Central nervous system. Cerebellum: degeneration of Purkinje cells and nucleus dentatus. Cerebrum: Neuronal degeneration and neuronophagia; cerebral edema.

Skin: Icterus, moderate.

Arteriolocapillary thrombosis, involving: skin; parathyroids; intestines; lungs; heart; lymph nodes, superficial and deep; spleen; liver; pancreas; brain; medulla.

Purpura, with involvement of: skin; pericardium; myocardium; larynx; lungs; stomach; intestines; pancreas; adrenals; kidneys; urinary bladder.

Cause of death: Thrombohemolytic thrombocytopenic purpura.

The heart was enlarged (465 Gm.) The purpura which was noted in the skin during life was also present in the mucous membranes, in the larynx, and gastro-intestinal tract. However, the most important changes were seen best under the microscope.

A section from the myocaridum shows the pathognomonic diagnostic change. (Fig. 1). Here is a blood vessel which is occluded by a homogenous pink staining, amorphous material, in which one can see a few cells. You will see later that the whole body of this patient was riddled with similar occlusive vascular lesions of this type. Special studies reported in the literature demonstrated that this lesion is at the arteriolo-capillary junction. According to some the lesion is a platelet thrombus. An important study of this condition was contributed by Dr. Gore, a former member of our department.

Histochemical studies would seem to support the platelet thrombus nature of the lesion. Some authors centrifuged masses of platelets, stained them, and obtained histologic and histochemical reactions which are practically identical with those seen here. It is probably true that these are platelet thrombi, but in addition there is something else. In the lesion seen in the next slide, at a higher magnification, endothelial cells are seen in some places and not in others. (Fig. 2). Observations like this have been interpreted as evidence that the primary lesion is in the blood vessel wall. Consequently there may be an increased permeability which leads to some kind of transudation in this area. The endothelial lining is pushed into the lumen. Later on as the lesion progresses, reactive fibroblastic changes are seen. Lesions of this type, of various ages, will be shown in our patient. A significant finding differentiates this condition from certain hyperergic lesions, such as, panarteritis, namely, there is no evidence of an inflammatory reaction. The location of the lesion is also important. It is at the end of the arterioles, where the muscular coat disappears, at the junction between the arteriole and the capillary.

Interstitial hemorrhages were present in the kidney and in the adrenal. Interstitial hemorrhages are not present in all cases. One author in a paper published in 1955 stated that in his own material and in the literature reviewed by him the interstitial hemorrhages were rather conspicuously absent. In our case they were prominent.

The spleen was enlarged and weighed over 400 Gm. The spleen was also the site of thrombotic lesions.

In Figure 3 we see the thrombotic lesion in the capillary of the glomerulus. This illustrates that location of the vascular lesion is not limited to the arteriolo-capillary junction.

Most of the lesions in the liver were in the periportal spaces. (Fig. 4 and 5).

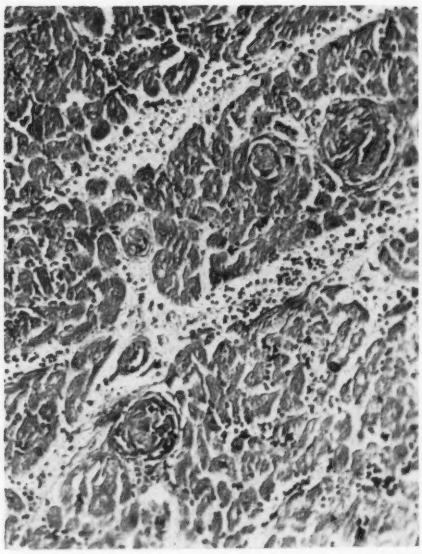

FIGURE 1: Heart. Several characteristic thrombotic lesions (140X).

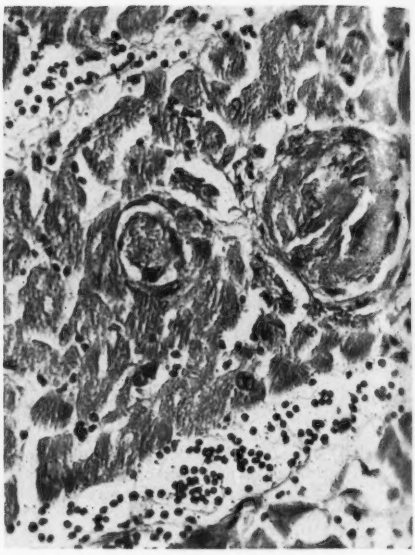

FIGURE 2: Heart. Higher magnification. Endothelial lining is distinct in the largest lesion. The absence of endothelial lining at the base of this lesion is clear-cut. (175X)

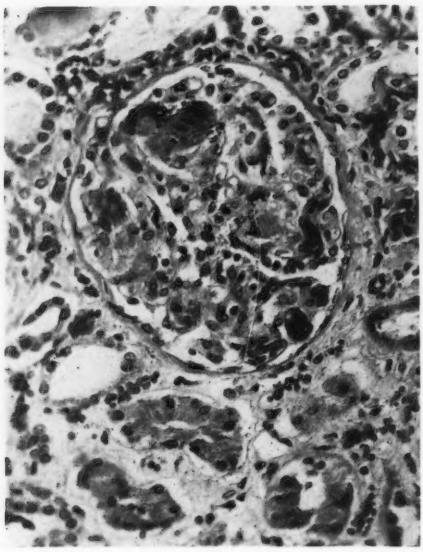

FIGURE 3: Kidney glomerulus. Capillary thrombi. (365X)

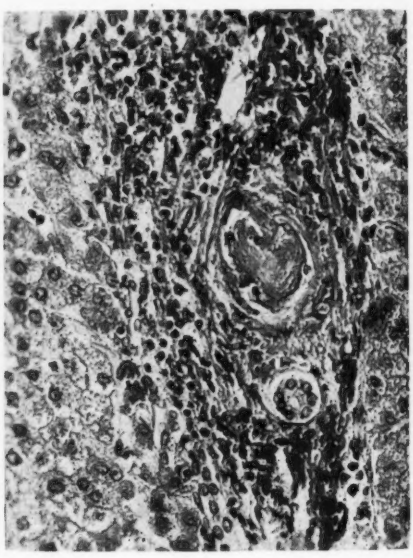

FIGURE 4: Liver. Vascular lesion in periportal space. (365X)

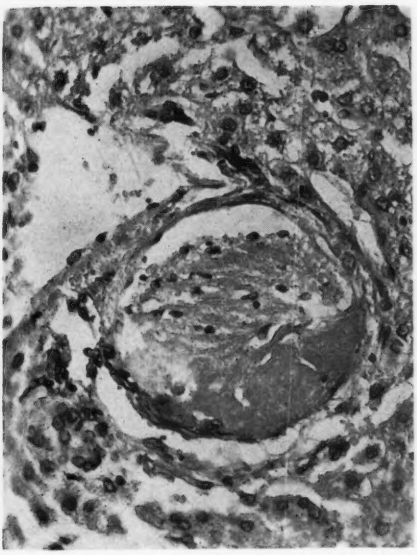

FIGURE 5: Liver. Larger thrombotic lesion with proliferating fibroblasts. PAS stain. (300X)

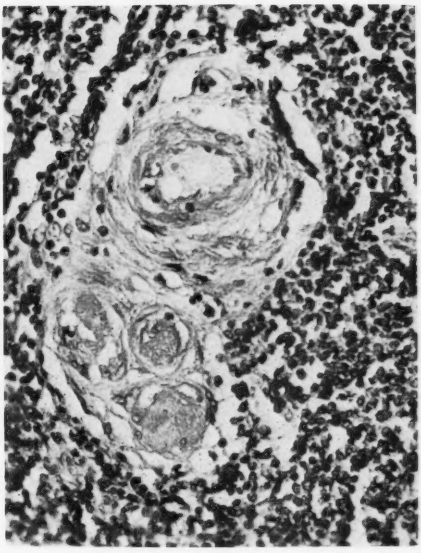

FIGURE 6: Lymph node. Thrombotic lesions of various sizes and ages. (365X)

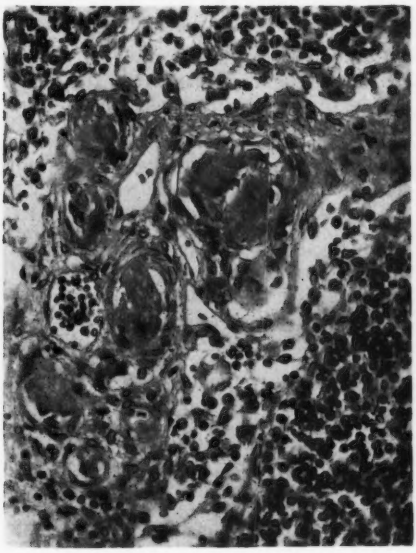

FIGURE 7. Lymph node. Three vascular lesions. The smallest appears to be considerably younger. (365X)

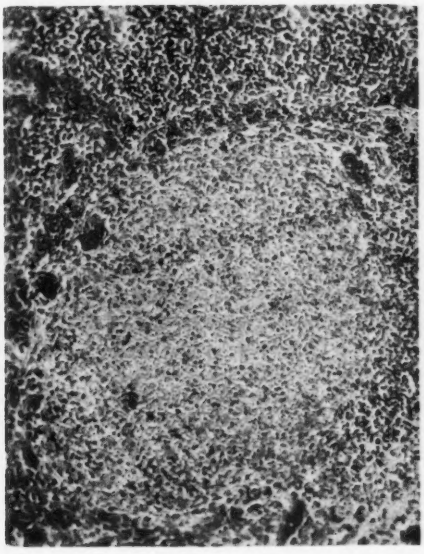

FIGURE 8: Lymph node. Focal necrosis occupying most of the field. (160X)

FIGURE 9: Brain. Thrombotic vascular lesion. (166X)

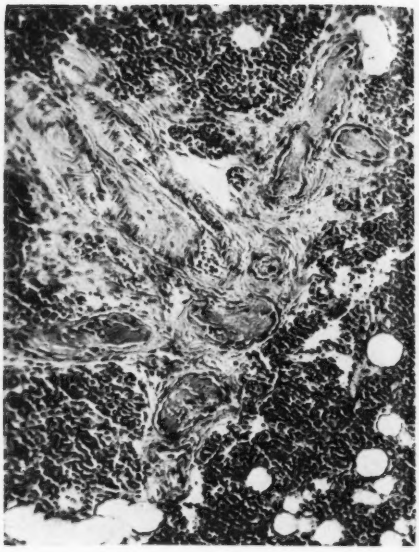

FIGURE 10. Parathyroid. Several vascular lesions. (144X)

The characteristic lesions were present in the deep lymph nodes, which were enlarged, and in the superficial lymph nodes, which at autopsy were not found to be enlarged. In Figure 6 we see what I think is a very early lesion with damage to the wall and encroachment upon the lumen with endothelial cells being present. Close by is an older lesion. In Figure 7 are many lymph node lesions in various stages.

As stated previously, a characteristic feature of this lesion is that there is no inflammatory reaction. The second characteristic, is that there is no tendency toward necrosis, for example, towards infarction of the heart muscle in spite of the many lesions in the heart. This is different from periarteritis nodosa. A case was presented at a conference, about 20 years ago, of a patient with periarteritis who died as a result of myocardial infarction. In Figure 8 is the only necrotic lesion that was seen in this patient, in a lymph node.

It was stated in the literature that lesions in the lungs are rare. We found many lesions in the bronchial walls.

Hemorrhages were present in the mucosa of the urinary bladder, of the larnyx and of the gastro-intestinal tract.

Lesions were present in the central nervous system, in the brain, and spinal cord, with degenerative secondary changes in the ganglion cells. (Fig. 9).

Many lesions were present in the parathyroid and in the intestines. (Figs. 10 and 11).

I venture to say that there were few tissues in which the lesions were not present. We were not able to demonstrate them in the bone marrow.

Small hemorrhages and the characteristic vascular lesions were present in the adrenal.

Discussion

Now a few remarks about the concept of the disease. What I am going to tell now is a combination of fact and fiction.

FIGURE 11: Small intestine. Several fairly recent thrombotic lesions. (140X)

It is somewhat speculative, because much of the condition is speculative.

It is remarkable that the disease was diagnosed during life with such readiness. The anatomic lesion is a "Disseminated arteriolocapillary junctional (possibly mural) lesion" which I consider as possibly autoimmune. Abnormal permeability is postulated. Subintimal transudation is less hypothetical. There is no doubt that the last word has not been said about the pathogenesis of the lesion.

The platelet thrombosis seems to be the basic lesion which accounts for a good part of the secondary changes modifying it. There is slight reactive proliferation, as evidenced by the proliferating fibroblasts, which may lead to organization. The lesion is not exudative, there are no inflammatory cells, it is nonnecrotic or rarely necrotic, as we saw it only in the lymph node, and even there I am not sure that it is what I would call a truly necrotizing lesion. There is aneurysmal dilatation. These are the things we know about the anatomic lesion.

The point of view presented here is summarized in Table 1.

The clinicians have done a fine job of analyzing the clinical manifestations, with the thrombocytopenia leading to mucocutaneous and interstitial purpura. The intermittance of the central nervous system manifestations is important. It may be explained on the basis that there are many capillaries in the body. Consequently many may be involved, without necessarily producing functional changes. Furthermore if some of them are involved, the others may be called into action rapidly. That may explain the intermittent character of the clinical manifestations particularly in the central nervous system. Next is renal failure which was beginning to become apparent in this patient. Finally, there is anemia and jaundice. The latter is related to the hemolytic, possibly autoimmune, anemia with intermittent spherocytosis.

In our case the characteristic findings were prominent, of course. There was acute overwhelming systemic disease, with purpura, anemia, and intermittent central nervous system manifestations.

The clinical-pathologic findings are important. They include: thrombocytopenia and hemolytic anemia. Marrow examination can help a great deal. It showed in our case megakaryocytic immaturity. In some instances in the literature, marrow puncture, and more successfully marrow biopsy, showed the characteristic thrombotic lesions. It may also be seen in lymph node biopsies.

Dr. Cardon referred to the possible therapeutic value of splenectomy. This approach is supported by the case report which was mentioned in the discussion. The patient in the report was alive for about 3 years, had clinical manifestations of the disease, and what is important, these lesions were present in the spleen that was removed. That, and what Dr Friedman had to tell us about the case in his experience, suggest that maybe splenectomy should be considered.

A study of this type is not complete without some reference to the history of

TABLE I

Thrombohemolytic thrombocytopenic (pancytopenic?) purpura
A Partly Speculative Concept

I. THE LESION

1. Disseminated arteriolocapillary
   Junctional (mural ?) lesion (autoimmune ?)
   ↓
   (Abnormal permeability ?)
   ↓
   Subintimal transudation (?)
   ↓
   Platelet thrombosis
   ↓
   Slight reactive proliferation; non-exudative, non-necrotic
   ↓
   Aneurysmal dilatation

2. Hemolytic anemia (autoimmune ?):
   Intermittent spherocytosis

II. THE CLINIC

1. Thrombocytopenia ↓ *Purpura* Mucocutaneous; Interstitial
2. Anemia; Jaundice

Intermittent CNS manifestations

Renal failure

III. DIAGNOSIS

Clinical Syndrome

Acute overwhelming systemic disease
  Purpura
  Anemia
Intermittent CNS manifestations

Clinical Pathology

Thrombocytopenia;
Hemolytic anemia;
Marrow puncture:
  megakaryocytic immaturity
Marrow biopsy:
  thrombotic lesion;
Lymph node biopsy

IV. THERAPY

(Splenectomy ?)

the disease. The best way to study a disease is to read the original paper and the latest review.

The first paper is by Moschcowitz in 1925[1], where he described the clinical picture. He called it "pleiochromic anemia with hyaline thrombosis". A good review by the late Dr. Karl Singer appeared in Advances in Internal Medicine in 1954[2]. Adelson wrote a more recent[3] review.

In spite of the short history of this disease, 32 years, there already had been time to suggest 10 different names for it. This is just the beginning. There may be more names coming. The oldest name was in Moschcowitz' paper. The sixth

term was suggested in a paper from our department, a case presented at a conference in 1948 and reported by Drs. Comess and Oyamada, where the patient had this condition complicated by uremia with necrotizing arteriolosclerosis. The term "thrombohemolytic t h r o m b ocytopenic purpura," which Dr. Rappaport selected for the autopsy report as appealing to him best, and I like it too, was suggested by Adelson in 1955.

Finally, a little more speculation on the possible role of sensitization. Certain features of the disease, the rapidity with which the clinical manifestations develop and the development of the anatomic lesions suggest that hypersensitivity may play a part. The possible role of exposure to X-radiation would have to be considered, at least as a synergistic factor.

TABLE 2

Thrombohemolytic Thrombocytopenic Purpura
Nomenclature

1. An acute febrile pleiochromic *anemia* with *hyaline thrombosis of the terminal arterioles and capillaries.* (Moschcowitz, E., Arch. Int. Med., *36*:89, 1925).
2. Diffuse, generalized, or disseminated platelet thromboses (Boehr et al, 1936).
3. Thrombocytic acroangiothrombosis (Fitzgerald et al, 1947).
4. Thrombotic thrombocytopenic purpura (Singer et al, 1947).
5. Disseminated thrombocytic thrombosis (Wyatt and Lee, 1950).
6. Uremia and *disseminated platelet-cell* (thrombocyte) *thrombosis* (Comess, O. H. and Oyamada, A., A.M.A. Arch. Int. Med., *89*:802, 1952).
7. Platelet thrombosis syndrome (Beigelman, 1951).
8. Moschcowitz syndrome (Lennox and Dacie, 1951).
9. Thrombotic microangiopathic hemolytic anemia (Symmers, 1952).
10. Thrombohemolytic thrombocytopenic purpura (Adelson et al, 1955).

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SOCIAL ASPECTS OF MEDICINE AS PART OF THE MEDICAL CURRICULUM

By THEODORE M. BAYLESS, M.D.* and G. J. SCHEFF, M.D., Ph.D.**

Medical education is constantly in a stage of transition, trying to measure up with the ever growing progress of medical science. As in so many other fields of endeavor, here also the technological advances far outstrip the social improvements. However, there can hardly be any doubt that a definite trend is developing towards the recognition of the social phases of medicine. Hence, this trend will have to be reflected in medical teaching before long.

To avoid misunderstandings, it should be emphasized that social medicine and socialized medicine are not to be considered synonymous. We wish to limit our discussion to "humanism" in medicine without any political implications.

Factors which stress the need of social medicine: It would seem that as a result of scientific detachment, or objectivity, which permeates our medical education today, the importance of social, environmental and emotional factors in the development of many illnesses and their integral role in treatment have been overlooked. This coincided with changing practices in medicine such as the shift from the home to hospital care and increased reliance on laboratory diagnosis. Specialists and physicians in group practice have arisen to replace general practitioners.

All these changes distracted from effective medical practice, since the family doctor had the best concept of the needs of the patient as a person in his own individual setting. Many other factors, such as family background, personality problems including anxieties, attitudes, prejudices and intolerances are known to contribute to illness and hence require proper integration when dealing with a disease entity.

But beyond this, the truly social problems should be concerned with financial problems, cost of medical care(particularly in chronic illness), educational problems, family and marital relationships, occupational adjustment, etc. We must learn to recognize, understand, evaluate and apply these social and economic factors to medical problems.

At present the training in the social and economic aspects of disease are very limited in scope and practical experience. It has repeatedly been pointed out that the poor premedical preparation of most students in the social sciences is perhaps the reason for the lack of interest and difficulty in teaching these factors. No doubt a broad background in sociology, psychology and philosophy would pave the way for easier acceptance of such ideas.

The premedical education should include: a study of the structure of society; the functions of the family, community and government; the role of the voluntary community agencies; and the place of the patient in society. Students must also gain insight into various aspects of human behavior, such as personality development and the psychology of sickness. Other equally important items are the understanding of the morals and emotional reactions of various ethnic and religious groups, particulary as they affect attitudes toward diet, illness, disability, medical treatment, and death.

Formerly, when medicine was taught by apprenticeship, there was less need for special courses in the social aspects of medicine. But, as we mentioned earlier, the scientific exactness of medicine today has resulted in slighting of the social and economic factors involved

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in disease. The medical student is likely to be impressed with the importance of making a diagnosis and then treating the patient medically or surgically. However, the importance of home environment, nutrition, personal and cultural attitudes in the etiology and management of the disease also needs to be stressed by the medical instructor.

There is a definite need—at times—to take the medical student out of the academic environment of the large medical centers and hospitals and into the atmosphere of the native community. The hospital patient removed from his home environment and placed in abnormal surroundings is psychologically a different individual. It is, indeed, difficult to evaluate the varied influences and problems of the environment as they effect the patient as a person. Also, the impending need for emergency decisions, and the emotional adjustment to unexpected disease is not seen by the medical student in his contact with a hospital patient. In the home surroundings one can see or sense the impact of the family and all other contacts on the patient without his conscious readjustment. In other words, the students must see the family as a social and biological unit. Where one of its members is involved in difficulties, all are involved.

There are, however, other considerations also. With the possible exception of pediatrics and obstetrics, the hospitals and outpatient clinics provide little or no exposure to healthy people. Students are accustomed to dealing with ill or incapacitated persons, and find it difficult to deal with minor complaints or non-hospitalizing illnesses. Healthy or only slightly ill people require a different kind of mental rapport. The sense of compassion often felt with chronically ill patients is missing and thereby the confidence towards the physician is weakened. This presents a new challenge for the student.

Living in a highly competitive society always presents many difficulties. It is most regrettable therefore, that medical students have little opportunity to appreciate the economic aspects of medicine and the limits that economics place on practice. On one hand, it is hard for the student to visualize medical practice without all the diagnostic and therapeutic facilities as they are available at most teaching hospitals; on the other hand, most students have a very poor concept of the appalling conditions prevailing in the indigent population.

In order to overcome these misconceptions, the student should have the opportunity to observe a family in its normal daily routine without disease or incapacitation. As an unbiased observer he could learn to appreciate the economic, social and emotional problems of the family. This knowledge will be invaluable to him later as an intern, resident or practicing physician.

Similarly, the student has little knowledge of and much less experience about the available community resources, such as welfare agencies, public health departments, and employment bureaus. He must have knowledge of the teamwork which develops between these agencies and the medical staff and know how to properly utilize social consultation. Only by close contact can he acquire the skill necessary to handle difficult home and community situations.

Hence, many medical educators feel today that the student must see the family at close range. To put this into practice various methods have been proposed. Some of them have already been introduced on permanent or on trial basis in some medical schools. Besides the conventional, classroom and bedside teaching, they involve extramural projects and exercises. In general, these projects can be divided into 4 categories and shall be reviewed briefly:

1. Case Study Projects or Family Study Plans. They are usually under the auspices of the public health department with or without the participation of one or several of the clinical departments. Often, the instructor in charge has appointments in two departments, which facilitates the assignment of cases.

Although the year of instruction var-

ies, most of these programs are confined to the 4th year. Some are given in the 3rd and the 4th years. One school, the University of Pennsylvania, which we shall discuss later on more fully, has a 4 year elective program. Courses of this type are required in about 30 medical schools in the Untited States and Canada.

In most programs only one student is assigned to each case, while there are some which assign 2 or 3 students. It is felt that with multiple assignments the students may stimulate each other's interests. This practice also conserves student and teaching time which is already overtaxed, as well as assignment of cases. The main disadvantages in such a system are the variable interests on the part of the students and the lack of intimacy with the patient or his family. At some schools cases are chosen from the active files of the social service departments of the affiliated hospitals. At others the students choose their own clinical cases. The student seems to have more interest in a case of his own choice, but he may not always select the most instructive case, being attracted to diagnostic or therapeutic problems.

A study guide or working outline is usually provided for the student. These forms supply key questions not to be forgotten during inquiry. They also help the student to evaluate the findings. Most schools require the student to write a final evaluation of the assigned case and of the course.

The length of time allotted for such study varies, but most schools feel that the student needs prolonged contact with the patient because the evolution of problems is usually slow and the investigative pace is limited. The usual duration of assignment to one case is one to three months. Some schools feel this is inadequate and have extended the course to 1 or 2 years. The University of Pennsylvania course entails, as we shall see later, 4 years of frequent home visits. Other schools, like Vanderbilt and Cornell, have extended their courses to at least one year.

The majority of programs include discussion seminars in which students and faculty members participate. Individual progress meetings are also held with a faculty instructor or social service worker.

At this point, a short glance at the participation of the social services might be useful. It varies greatly in different schools. In general, their main function is to select cases and guide the individual students. A social worker may help the student to plan his study, tell him about available social resources, coach him before home visits, discuss with him arising problems, and help him to evaluate the social data collected during his study. The social worker may accompany the student and act as a liaison on his visits to the home and social agency. Some medical schools and teaching hospitals have well organized social service departments to meet the needs in these programs. At Cornell University the medical student is accompanied by a student social worker and a student public health nurse on his visits to the home; they file a joint report. Among other schools, which have extensive social service participation in case study programs, are the medical schools of Tulane University, New York University, the University of Pittsburgh, the University of Buffalo, and the University of Oklahoma, to mention only a few.

2. Domiciliary Service. These programs are somewhat narrower in scope and are intended to bridge the gap between hospital training and general practice. In carrying out this service, senior medical students make home visits in answer to calls of clinic patients for home medical care. The duration of these programs is only 1-4 months and they are under the supervision of preceptors. Individual conferences are held with the preceptors to discuss medical and social problems and observations. However, there is very little continuity of experience or guidance. Georgetown University and Tufts Medical School have such programs. At some other schools similar programs are in effect but are intended to supply medical care for the indigent population of the community, with little or no emphasis on

instruction of the students in the social aspects of medicine. Any knowledge gained is purely accidental through observation during these patient calls.

3. Home Delivery Service. These programs are no more than an extension of the prenatal care. At Vanderbilt University, for instance, public health nurses and social service workers accompany the student on home visits. The students thereby gain a limited exposure to indigent home environment. The Chicago Maternity Center conducts a similar program.

4. Preceptorships. These programs consist of assigning a student to a practicing physician or group of physicians so that he may participate in private medical practice. This includes home, office and hospital visits. Many programs of this type, as for instance at the University of Wisconsin, are conducted in small communities.

In 1954-55, 24 medical schools offered preceptorships in the United States. In some of these programs the preceptors were general practitioners; in others, they were reported to be specialists; while there were some in which both GP's and specialists participated. Most of the schools offered preceptorships in the 4th year, while a few were open to 2nd and 3rd year students also. They were required in 10 and elective in 14 schools. The length of time spent in preceptorships varied from 2 weeks to 4½ months.

The objectives in these programs seem to center on the desire to offer students an opportunity to closely observe medical practice as it is actually carried out. They offered the students an opportunity to investigate certain types of practice which they may desire to go into later. At the same time, they learn to appreciate the social, economic and environmental factors as they present themselves to the physician in actual performance.

A survey of the Educational Section of the American Medical Association expressed the opinion that "preceptorship programs deserve the over-all study and implementation which will make it possible to realize their maximum potentialities as part of an undergraduate medical educational experience."

As an illustrative example, the detailed description of the family study plan, conducted by the Family Health Advisor Service at the University of Pennsylvania School of Medicine, will be presented here. The course was established in 1949. It gives the student an opportunity for continuous contact with the same family throughout the 4 years of the medical curriculum.

The plan is under the auspices of the Department of Public Health and Preventive Medicine and the Department of Psychiatry. It is an elective course open to all freshmen. The student is assigned a family carefully selected by the Social Service Department. The families chosen live conveniently close to the hospital so that student travel time is kept to a minimum. Most of these families depend on the hospital for their medical care; only a few have private family physicians. The social, cultural and economic status of the families varies. Some are self-supporting while others are on relief. Seventy-five per cent or more of the families have children. Some elderly couples and persons living alone are also included.

Contact with the family is usually made through one of its members who has been either a patient in the hospital or an outpatient. For 4 years the student acts as a friendly adviser for the family, keeping track of all events, whether medical, economic or sociological; these include the growth and development of children and the effect of illness, injury or emotional conflict as they may arise. The student visits the family once a month if there is no illness, and more frequently if there is illness or trouble.

He is in a position to observe the sanitary level of the home and of the neighborhood, the availability of recreational opportunities, the inter-action of various members of the family as well as the presence or absence of emotional tensions and conflicts and their rebounding influ-

ence on the various members of the family. In emergencies, the student can call on a faculty adviser. A small group of students meets once a month for discussion with a faculty group (consisting of an internist, a pediatrician, a surgeon, a social worker, and a psychiatrist) to clarify and dispose of difficult problems.

This program bears fruit in many ways. Through personal contact, the student soon becomes conscious of the actual problems of life and death. He comes aware of the difficulties of establishing satisfactory relations between the doctor and his patient and of the detrimental effects of failure to do so. He is encouraged during his own maturation process to gradually assume more responsibility. He does that, not in the capacity of a physician, but as an important link between the hospital and the family. He develops a better understanding towards the community health agencies that touch upon the health needs of his assigned family.

This course seems to supply practical and vivid motivation for learning. It gives the perspective the family doctor used to have. The importance of family, home, economy, and sociology is better appreciated, not through lectures, but by actual experience.

In conclusion it can be said that the various programs all stressing the social aspects of medical education are not yet perfect — advantages and disadvantages balancing each other — but certainly they are an experiment in the right direction from which gradually a better medical training program will emerge.

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